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FATTY DEGENERATION OF THE INTIMA OF ARTERIES

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(From the Pathological Laboratories, University of Pittsburgh, Pittsburgh, Pa.)

Reprinted from
The Journal of Medical Research, Volume XXXII., No. 1
(New Series, Vol. XXVII., No. 1), pp. 27-43, March, 1915

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FATTY DEGENERATION OF THE INTIMA OF ARTERIES.*

OSKAR KLOTZ.

(*From the Pathological Laboratories, University of Pittsburgh, Pittsburgh, Pa.*)

The tendency for the arterial tissues to undergo a fatty degeneration,† and the importance of the process in the pathogenesis of arteriosclerosis, has been repeatedly commented upon, but different views have been taken on the immediate part which the degeneration plays in relation to other tissue changes of the arterial coats. Moreover, no unity of opinion has been reached as to the tissues which suffer this degeneration, or in indicating which type of cell, in the state of degeneration, is of prime importance in bringing about serious structural alteration, the end result of which is commonly discussed as atheroma. Prior to Virchow's classification of the fatty changes in the arteries, these were all discussed under steatomatosis, a term which was not alone applied to fatty degeneration of the arteries, but also to similar tissue changes of the organs. To-day in making the pathological distinction between fatty degeneration and infiltration, this term has been dropped.

Desirable as it may be to make a firm distinction between fatty degeneration and fatty infiltration of all tissues showing the accumulation of fat or lipoid bodies under pathological processes, difficulty is yet encountered in differentiating a hyperphysiological process from truly pathological degeneration. All tissue cells are not equally active or sensitive in dealing with fatty materials in their nutrition, some being unusually prone to indicate a slight intra- or extra- cellular disturbance by the accumulation of granular or globular fat in their protoplasm. Such unusual overloading of their protoplasm by foreign fat may occur without any demonstrable degenerative processes in the cell structure. On the other hand, the presence of fat within a cell which otherwise also

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* Received for publication, Oct. 14, 1914.

† The term fatty degeneration is used to indicate the abnormal accumulation of Sudan staining substances in cells and tissues.

shows processes of decomposition in protoplasm or nucleus, may be accepted as indicative of a true fatty degeneration, in the sense that the metabolism of fats cannot be properly accomplished in the functionally incapacitated cell. It is probable that the accumulation of fat in excess, in the tissues of the arteries, owes its presence both to true degenerations as well as to processes of a hyperphysiological nature. On the other hand, an accumulation of fat may occur within a tissue, in which its presence is not associated with cell activity or inactivity, but in which the living cells play no direct part, the fatty materials accumulating in the vitally inactive intercellular substance through chemical affinity. These extracellular deposits play no small part in the localization of lipoid masses in the arterial walls. We have recently pointed out the affinity of old amyloid deposits for fat, a process which appeared in part physical rather than chemical. We will later refer to a similar affinity for fat possessed by the hyaline intercellular substance of chronic endarteritis. In these latter instances, the fat is found to deposit only as the tissue changes of the vessels have passed from one state to another, until the nature of the degenerative process is such as to attract fat or lipoid bodies to itself.

In the arteries the important tissue changes associated with the deposit of fat occur in the intima. The muscle cells of the media may also show fat granules in their protoplasm, and, in fact, demonstrate these in the aorta of all individuals over fifty years, but no such important significance may be attached to this medial degeneration as a similar process in the intima. Virchow made a distinction between the superficial fatty deposits (fatty degeneration) of the intima and atheroma. The former he claimed was a process of fat accumulation within cells which remained superficial, while the latter was destructive and deep, lying upon the inner zone of the media. Jores has pointed out, and we believe rightly, that the distinction thus given is superfluous, and that many areas of superficial fatty changes may continue to increase and by the development of a fibrous plaque over the surface, come to take a deeper position from the vessel lumen. It is quite probable that not a few atheromatous processes have their beginning in the superficial fatty streaks which are so prone to develop in the course of acute systemic infections. It is of importance, however, to indicate that not all superficial fatty streaks, particularly of the aorta, give rise to atheroma, for prominent and common as these are in acute infectious diseases (typhoid fever, septicemia, pyemia) and intoxications (following extensive burns, cholemia, uremia), they in great part disappear upon recovery from the acute illness. The problem of the permanency of these degenerative lesions is to a great extent associated with the nature of the process, and, as we shall point out later, superficial fatty streaks in which the fat is found within the protoplasm of tissue cells, disappear much more readily than masses of lipoid materials in the interstitial substance or in the elastic or connective tissue fibers. Where fat accumulates in undue quantities within cells, which though degenerated are still living, the subsequent disposal of it is controlled by the cell. After removal of the noxious agent the cell on recovery utilizes or discharges the fat in a form which does not localize in its vicinity. On the other hand, the presence of fat or lipoid substance in the relatively inactive tissue fibers or in the tissue spaces, is disposed of only by chemical combination, less frequently by decomposition, through the agency of the tissue fluids. Soluble compounds may be the result, but too frequently insoluble compounds with calcium (Klotz, 1905) are the result. It is mainly this which determines the development of atheromatous masses from the superficial fatty streaks. We would thus prefer the use of the term fatty degeneration (as regards arteries) for those processes in which an undue amount of fat is present within cells or their fibrillar processes, while the term atheroma may be applied when the fat lies free in the tissue spaces where it may be recognized both macroscopically and microscopically as a smeary, gruelly mass. From the very nature of the process where cells have undergone fatty degeneration with subsequent death, the atheromatous area not alone contains the fat substances of the cells, but also the protoplasmic detritus of their bodies. The composition of the atheromatous deposits is hence very mixed, while the lipoid contents of the living cells is relatively simple.

The importance of fatty degeneration in the intima of arteries, though commented upon by all investigators of the subject of arteriosclerosis, was particularly emphasized by Jores. For him, fatty degeneration of a distinct form was an essential part of arteriosclerosis, and conversely it is to be taken from his attitude that arterial lesions lacking this process are not to be classed as arteriosclerosis. In his earlier work (1903) upon which the present-day definition of arteriosclerosis of his school still rests, he indicated that the essential features of arteriosclerosis are a splitting of the internal elastic lamina and a hypertrophy of the longitudinal muscle layer accompanied in all instances by a fatty degeneration of these muscle cells. Connective tissue proliferation may subsequently invade the damaged musculo-elastic layer or give rise to a plaque over the areas of degeneration. Fatty degeneration of the intima he claimed was always primary in the deep muscle layer and was never primary in the superficial connective tissue plaque of the intima. This we have found to be erroneous, and being so, seriously opposes the narrow and incomplete viewpoint of the pathogenesis of arteriosclerosis as defined by Jores.

In the intima we have found that every type of cell and tissue normally present in this structure may undergo fatty degeneration and, what is more important, may show this degenerative process in the absence of any constant preceding lesion. Thus at times the elastic fibers, the muscle cells, the connective tissue cells, the connective tissue fibers or the lining endothelial cells may first show deposits of fine or coarsely granular fat in their substance, and, in a recent analysis of the intima of the aorta in the vicinity of the intercostal arteries, we have been surprised to find the frequency with which the connective tissue cells and fibers have contained fatty materials in the absence of degenerative change of the deep muscle layer. This is true also for the elastic fibers, which may undergo an alteration in their composition with the gradual impregnation by fatty substances. There is, however, another type of cell which appears to be foreign to the normal intima, but which under conditions of disease makes its appearance in the superficial or even deep portion of the intima and is characterized by an abundant fat content of its protoplasm. Recently this type of cell has received particular attention by those studying the experimental intimal lesions induced by feeding cholesterin mixtures to herbivorous animals. By Anitschkow it is referred to as the "cholesterinesterphagocyte," while we have spoken of it as an endothelial or lutein-like cell. This cell deserves special attention as it is a common structure in human arteries and may be present in such numbers and clusters as to be recognized by the naked eye.

Fatty processes of various kinds are not alone of importance because of their frequent presence in different types of arteriosclerosis, their association with the development of atheroma, the variety of tissues attacked, but also because they constitute a type of change which, after middle life, is constantly found in the muscle tissues of some of the arteries, and indicates a diminished functional capacity of the vessel wall. This is particularly true of the aorta, where on the whole fatty degeneration both of the intima and media are more frequent than in the peripheral vessels. Moenckeberg reported the frequent finding of severe medial disease of the peripheral arteries in which no evidence of fatty lesions of the intima were to be found. Likewise Hallenberger found an absence of fatty change in the intima of the radial artery even where this inner coat was greatly thickened. Similar observations are reported by Jores, where the intima was thickened under a process of "connective tissue hypertrophy" or true endarteritis. We have also noted the presence of moderate and even severe intimal thickenings in which no demonstration of a fatty degeneration was possible, but we can by no means assert that these proliferative processes without degeneration are unique in their pathogenesis or structure, which differentiates them from those with fatty change. Regardless of the associated structural alteration which may accompany, precede or follow the fatty degeneration of the intima, the deposit of fat within the cells or their fibers is the result of a nutritional change, an asphyxia, or an intoxication, and in the different cases the damaging factor is very various. In some cases fatty degeneration may be a very early sign, in others only a very late one. Bacterial intoxications, though not even constant with the same organism, may lead to an unusual fatty degeneration of several kinds of cells in the intima with very little evidence of a proliferative reaction (typhoid). In others again, where the tissue response is slower, as in syphilis, and where a proliferative reaction of the intima is accompanied by the development of new capillaries from the vasa vasorum and only follows the medial disease, relatively little evidence of fatty degeneration is found. The commonly recopied statement that no fatty degeneration occurs in the syphilitic endarteritis is incorrect. Microscopical analysis of such lesions will demonstrate in the majority a greater or less amount of fat in the newly developed connective tissue cells, their hyaline interstitial substance as well as in the greatly altered elastic fibers. It is seldom, however, that the degeneration leads to the liberation of such quantities of fat as to constitute atheroma.

To Jores we are indebted for pointing out that the muscle fibers of the deep intima which undergo hyperplasia, in response to a prolonged increase of the blood pressure, are very liable to fatty degeneration. It is in fact this combination of circumstances which, along with the splitting of the internal elastic lamina which bounds them, constitutes for him arteriosclerosis. The liability of tissues, after undergoing extensive hyperplasia in response to a continuous acting cause, to suffer degenerative processes may be observed in a variety of structures of the body (kidney, heart, liver). It is probable that the work-hypertrophy which appears in the musculo-elastic layer in response to the greater circulatory stress thrust upon the vessel walls, suffers fatigue, when owing to the limit of hypertrophy in relation to the available local nutrition, having been reached, the hyperplastic tissues suffer an asphyxia and starvation. These hyperplastic processes of the musculo-elastic layer are not accompanied by any increased vascularity of the tissues but it is probable that the not uncommon connective tissue overgrowth, which becomes associated with this process, still further interferes with such nutrition which the intima obtains from the lumen of the vessel. We have in several instances observed the presence of fatty degeneration of the cells of the intima and the inner layer of the media, opposite a complete thrombosis of the arteries of the extremities, while in the peripheral parts of the arterial coat, as well as in the artery lying proximal to the point of occlusion, evidence of a fatty change in the tissues was wanting. By this it is suggested that the arterial wall is in part at least dependent for the nutrition of its inner layers upon a direct absorption from the lumen of the vessel.

By whatever means the tissues of the intima suffer and tend to accumulate fatty materials, be it through the harmful action of bacterial toxins (B. typhosus, streptococci), exogenous or endogenous poisons (tobacco, lead, adrenalin, absorption products from severe burns), mechanical stress (high blood pressure) or direct nutritional disturbances, the process may be best understood in the light of an asphyxia of the cellular elements. In each instance the functional activity of the cells is depressed to a degree that a proper intracellular metabolism is no longer possible. The fatty materials brought to the cells in a state of solution are absorbed but not completely worked over, with the result that the unfinished products form a deposit within the cells. Obviously some tissues are more easily influenced by certain factors than others, and will hence show the presence of this abnormal product at an earlier period Nor do we always find the cells exhibiting fat in the same order or sequence, for at times the muscle, at others the connective tissue or the lutein-like cells may first demonstrate the deleterious influence of the particular agent. At all times, the particular agent and its selective action upon tissues, as well as the intensity of its influence, must, to a great extent, determine the character of the degeneration.

In the human subject the surface endothelium of blood vessels commonly shows the presence of fat in acute inflammation. Particularly is this noted in the small arterioles and capillaries in the vicinity of an acute or subacute reaction, and may be observed in appendicitis. Such evidences of fatty degeneration appear to have little significance and rapidly disappear after healing has been complete. It may be suggested that the granules of fat have been phagocyted by these cells, but in the absence of similar deposits in distant parts, it may rightly be assumed that these cells have been influenced during the inflammatory process to alter their functional activity. Seldom do these deposits of fat amount to more than granular accumulations about the nucleus, and their presence is only recognized by the microscope. Under similar conditions, but particularly in the presence of subacute and chronic inflammation, is observed an endothelial type of cell which becomes loaded with a simple form of fat. These cells we have recently described arising in the intima of the aorta during processes of connective tissue hyperplasia. They are endothelial in character in as far as the cells are large with a centrally placed nucleus and a wide protoplasmic border. The nucleus is round and stains quite distinctly. The protoplasm appears granular or vacuolated when treated with alcohol, and resembles the character of the lutein cells. We are, in fact, of the opinion that these cells bear a close relation to similar large cells found beneath the peritoneum as well as in the musculature of the Fallopian tube during chronic inflammation. It is not probable that these lutein-like cells have an association with the lining endothelium of the blood vessels. Their nuclei are smaller and stain more intensely, and the protoplasm is decidedly more granular. The fat content, too, is much greater and its distribution is uniform, not being isolated to the vicinity of the nucleus. True phagocytic properties have not been observed in association with this type of cell. Anitschkow suggests a lymphocytic origin to these cells.

Up to the present the lutein-like cell has been most frequently encountered in the intima of the aorta, but has also been observed in areas of fatty degeneration of the peripheral vessels. Their presence is with difficulty determined in transverse sections through the arteries, where they may easily be confused with swollen connective tissue cells. When early (preferable to late) areas of superficial fatty degeneration are cut on the flat these cells may be observed in clusters, either near the surface or in the connective tissue layer close to the internal elastic lamina. The closely packed clusters show no evidence of stroma but appear to form groups lying in large spaces (Figure 1). These cells contain such an abundance of fat that their walls are indistinct, and the nucleus is frequently overshadowed, so that groups of these cells may be mistaken for atheromatous areas with only extracellular fat. Alcohol treated sections will demonstrate the individual cells in the groups as well as the spongy character of the protoplasm.

The origin of these cells is still indefinite, but they play an important part in the development of the fatty streaks of the aorta, as well as the subsequent atheroma arising from a breaking down of their cell bodies with the liberation of free fat into the interstices of the tissue.

We have observed these cells under conditions of inflammatory hyperplasia of the intima, but have missed them where pure hyperplasia of the musculo-elastic layer of the intima alone was present. Moreover, we have never found them in the deep media or the adventitia. Their presence in the connective tissue layer of the intima alone, and particularly under conditions of reaction where this layer is in a process of hyperplasia, suggests their development through the influence of an irritant acting upon the inner coat of the artery. The presence of these cells in the same tissues of animals under experimental conditions is of great interest. Ignatiobraski, Anitschkow, Saltykow and others have found similar cells in the aorta of rabbits when fed with cholesterin containing food. Under these circumstances fatty plaques appear in the intima which are to a great extent made up of lutein-like cells. In the early stages the fatty compounds within these cells have doubly refractile characters, and undoubtedly in part at least, the double refractile bodies observed in atheromatous masses have their origin from these structures.

In the human arteries, however, evidence of fatty degeneration not only occurs in this peculiar type of cell, but also in the connective tissues themselves. We have never missed its presence, in at least microscopic quantities, in the aorta showing even the earliest hyperplasia when the connective tissue thickening was associated with the occurrence of the large endothelial-like cells. Whether, as is suggested by some, there is a genetic relation between the connective tissues and the cells above described we are not able to say at this time. The degeneration of the fibrous tissue cells has the character of a fat deposit in the protoplasm, not only in the body of the cell, but also in its stellate processes (Figure 2). The fat is in the form of granules or small globules which do not coalesce, and which, even when the quantity is of fair amount, does not bring about a distortion of the cell body. The position of the nucleus remains unaltered. Hence, when cut on the flat, the connective tissue cells of the intima may always be distinguished by their morphology from other types. The character of the fatty degeneration here closely simulates the appearance of degenerating connective tissues grown in vitro.

These processes in the connective tissues of the intima also constitute a type of superficial degeneration which may be recognized on the inner surface of arteries as yellow streaks. Seldom do these cells show complete disintegration to form atheroma, save when they become involved in the border of a previous area of softening, and it is more than probable that a complete recovery from the process of degeneration commonly occurs. As these cells lie as a loose thin layer beneath the endothelium, the fatty materials are not aggregated at one point, and the macroscopic appearance of the condition is rather more diffuse than sharply defined. These degenerations are particularly frequent in the aorta suffering the early stages of endarteritis as we have elsewhere described. This early inflammatory process, provoked by bacterial toxins as well as the absorbed poisons of tissue disintegration (extensive burns), is a lesion of the subendothelial connective tissues in which infiltration, proliferation, and degeneration may go hand in hand. It is in these, particularly, that the fatty degeneration of the connective tissues may be found (Figure 3). On the other hand, that form of endarteritis developing as a secondary reaction over deep atheroma may in its early stages not show fatty change. But in this latter type, developing as a slowly progressive sclerotic plaque another form of fatty degeneration of the connective tissues is not uncommon. Here the fibrous tissue is very sparse in cells and nuclei, but the mass consists of a dense aggregation of fine fibrils which have a homogeneous appearance. It is difficult to trace the individual fibers, as the intracellular substance is very abundant and of a hyaline character. Occasionally much flattened and spindle connective tissue cells are found to contain a few fat granules at the ends of the nuclei. Whereas, in the new connective tissue cells fat is seldom found in the fibers or the interstitial substance, the presence of this substance in the hyaline plaques is quite common. The interstitial substance and the fibers undergo definite chemical change by which the hyaline appearance of the areas is produced. In this state there appears to be a greater affinity for fatty materials through which the hyaline area becomes impregnated with fat. The fat which localizes in the hyaline plaques does not appear to owe its presence to cell activity. It forms a slight and diffuse impregnation of the area which, when stained with Sudan III., gives a washed appearance with the presence of very few granules. At other times the fat appears in wavy strands, not sharply demarcated, but yet showing that the fatty material is in or upon an altered connective tissue stroma which lies parallel to the lumen and is thrown into folds by the contraction of the walls. Elastic fibers are not to be found in these areas, but in a layer which is disposed in lamellæ and which stains well with eosin. The deposition of the fat in this altered connective tissue stroma appears to bear some similarity to the deposition of fat and lipoids in old amyloid deposits. The diffuse fatty materials in the hyaline plaques of arteries appear as relatively simple fats and may be removed by alcohol, ether, and other fat-solvent agents. Its association with the hyaline groundwork is probably a physical or loose chemical combination.

The impregnation of fat into the hyaline connective tissue plaques has an important bearing not only because of the actual presence of this foreign material but in indicating a progressive process of degeneration which has attacked an area of fibrous tissue hyperplasia of the intima. It indicates that a slow destructive process may attack areas of connective tissue thickening, quite regardless of the nature of their origin. It is by the progressive increase of this process that atheromatous masses gradually involve more and more of the overlying connective tissue cap, until an erosion through to the surface has taken place — the atheromatous ulcer.

The elastic tissue of all parts of the artery may be subject to a fatty degeneration, but as Jores has pointed out, the most common and most important type is seen in the internal elastic lamina of the intima. Under conditions of disease of the media, the parallel lamellæ of that coat may show a similar process. Under most varied conditions do we find fat deposits outlining the innermost elastic band of the arteries. Both in the small arteries as well as the aorta and its branches may we observe this structure attacked, and at times it would appear that the greatest damage to the arterial wall at a particular point consists of a fatty degeneration of the intima. However, close observation will indicate that other reactions are also present, of which a hyperplasia of the intima, either of the deep muscle layer or of the superficial connective tissue lamina are the most common. The presence of fatty deposits in the internal elastic lamina is not to be viewed as an individual process, but rather as an indication of a previous alteration of the elastic structure by which its normal characteristics have been destroyed, so that it no longer reacts in a normal fashion to stains, but has acquired the chemical property of localizing fatty materials in its substance. The morphology of the elastic lamina is altered as has been described by Dmitrijeff, Jores, Fisher, and others. At times the lamina is granular so that its continuity is broken, leaving spaces in which the non-staining strands or fibrils of the elastic substance are seen; granules may appear along the inner border of the band (Aschoff), and particularly when an inflammatory reaction lies beneath the endothelium; the lamina may be broken up into fine fibrils, so that the appearance of a loose untwisted rope is obtained. In the last type the stain for elastin is wanting or is obtained very poorly. The appearance of the structure suggests a loss of the interfibrillar substance with its elastin content, so that the fibrils of the elastic bands are liberated, forming the loose striated bundle. It is probable that the brush-like appearance to the so-called ruptured elastic lamina has its explanation in a similar process. The bands have not mechanically ruptured, but a loss of continuity of the stainable material results, with, at times, a destruction of the fibrillar components of the elastic band, with the result that the partly disturbed elastic fibrils form brush-like extremities. All of these types of change of the elastic fibers, and particularly those resulting from a chronic course in which complete loss of the tissue constituents does not occur, may be accompanied by the deposit of fatty materials. Sudan III. picks out the affected areas very sharply and it is not uncommon to find an altered elastic lamina showing the only fat deposit in the artery. Here again, as in the accumulation of fat in the hyaline stroma of the connective tissue, the deposit depends upon a chemical affinity of the products of primary degeneration and not upon any direct cell activity.

Elastic fibers (internal elastic lamina) showing the presence of fat in their substances are, as above stated, not normal in their morphology or composition. The staining reactions are sufficient proof for the latter. The tendency to enlarge in their diameter, to show their internal fibrillar structure and the separation of many fasciculi is an evidence of the former. It is suggested that an altered nutrition (Jores) or the changes induced by the undue stress of work, as well as the direct action of toxins (Katsurada) or poisons may so affect the elastic tissue as to bring about these appearances. Those changes observed in them under conditions of inflammation are to be classified under toxic effects, taking place synchronously with the inflammatory reaction.

As the degenerative processes of the elastic fibers of the arteries are so commonly associated with the accumulation of fat, it is quite easy to follow the different stages in the disintegration of the elastin materials by means of special stains (Weigert, Verhoeff, Sudan III. and others). The definite chemical change in the composition of the elastic structure and the character of the fat deposit suggests that the accumulation of lipoids in amyloid, hyaline and elastic structures is closely related.

We have previously mentioned the occurrence of a fatty degeneration of the muscle elements of the deep intima (Figure 4). The actual evidence of fatty bodies in the intimal muscle elements themselves is not commonly observed, for it is only seen by those who search carefully the vessels of middle-aged people and who have the good fortune to obtain specimens in which the longitudinal muscle cells may be unmistakably differentiated. The mere presence of spindle-shaped cells in the region of the musculo-elastic layer even though those cells show fatty degeneration is insufficient to make a diagnosis of degenerated muscle cells. Lately through the influence of Jores' work we have, without further verification, spoken of all forms of fatty degeneration in the deep portions of the intima as of this type. We would here repeat that, although it has been amply demonstrated that a proliferative response on the part of the musculature of the arteries, and particularly by the muscle elements of the deep intima, occurs to physical and mechanical stress (increased blood pressure) and that processes of degeneration are liable to develop in the hyperplastic layer, we must also appreciate, as we have above described, that several other tissues also suffer a similar reaction, and when lying near the musculo-elastic layer may lead to much confusion in the pathogenesis of the lesion. In short, we can by no means assume that deep degeneration of the intima is necessarily a process in the musculo-elastic layer, nor that such reactions are indicative of a common causative factor. That atheroma may result from deep muscular degeneration of the intima (Jores) as well as from a similar lesion in other tissues of the intima we have indicated above.

Thus it is seen that a degeneration may involve every type of tissue in the intima. Nevertheless, our interest is stimulated as to the frequency and importance of the processes, as well as the relation of the lesions to arteriosclerosis. It has been our finding that endarteritis of true inflammatory origin both in its subacute and chronic stages is accompanied by fatty degeneration of the connective tissue, the endothelial or lutein-like cells as well as the elastic fibers, while reactions of hyperplasia of the deep muscle layer associated with unusual functional activity and with intermittent high blood pressure are also prone to suffer similar changes. Hence in considering both forms of response, arising in connective or muscle tissues associated with fatty degeneration, as types of true arteriosclerosis, the important bearing in the recognition of each is readily appreciated. Both types may advance to atheroma and its accompanying process of calcification and "ulcer."

The difficulty in recognizing the exact type of cell involved in the degenerative process is not so great in the smaller arteries as in the aorta, in which the intima is a complex structure. We have found, however, that by the method used in this study, of preparing the microscopical sections by making flat sections from the inner surface of the artery, a much better picture of the relation and character of the cells was obtained. The features of fatty degeneration of the intima, as we have described above, are then readily recognized.

The stage at which the fatty degeneration makes its appearance in the arterial coat is dependent upon the factor inducing the lesion as well as the character of the reaction in the wall. When by a process of high blood pressure there develops a hyperplasia of the deep intima, the fatty degeneration appears as a secondary process in the nearby muscle cells, as has been described by Jores. These newly developed muscle cells so alter their environment that nutrition is not available in sufficient amount and it may be that "overstrain" and "stress" (Adami) as the causative factor plays an important part in acting upon this tissue. These factors, purely nutritional and mechanical, can and do lead to this form of degeneration. On the other hand, active agents of a chemical nature (bacterial toxins, poisons, protein decomposition products) may directly influence the tissue cells with the accumulation of fatty materials within the cells. In the case of selective poisons, particular types of cells may be picked out and show the fatty change, or when the irritant induces inflammatory reactions, the tissues acted upon may synchronously show the presence of an exudate and the intracellular deposit of fatty granules. Even in the early stages of endarteritis where fatty degeneration is already present, it is often very difficult to indicate the sequence of change, particularly to determine at what stage in the reaction the fat made its appearance. There appears to be a type of reaction in the intima of arteries in which a connective growth is secondary to the fatty process. It has been shown (Jores) that where fatty degeneration of the deep muscle cells leads to the liberation of the fatty material and the development of an area of atheroma, a cap-like thickening of connective tissue gradually forms over its surface. The response in the connective tissues is not accompanied by an inflammatory infiltration, nor does this new layer contain elastic fibers. Here we must admit that in respect to the endarteritic plaque the fatty degeneration has been primary. In nearly all other cases of fatty degeneration of the intima the process develops either simultaneously with or secondary to other tissue reactions of the arterial wall. Thus, in truth, whether the important factor in arteriosclerosis is of a mechanical, bacterial or chemical character, the degenerative reactions in each play an important part in the progress of the disease. In the late atheromatous softening, with its complex chemical constituents, the deposition of calcareous salts is directly associated with the presence of these fatty bodies. Such atheromatous areas have their beginning in and their progressive enlargement due to the destruction of a variety of cells which by disintegration liberate their fat content.

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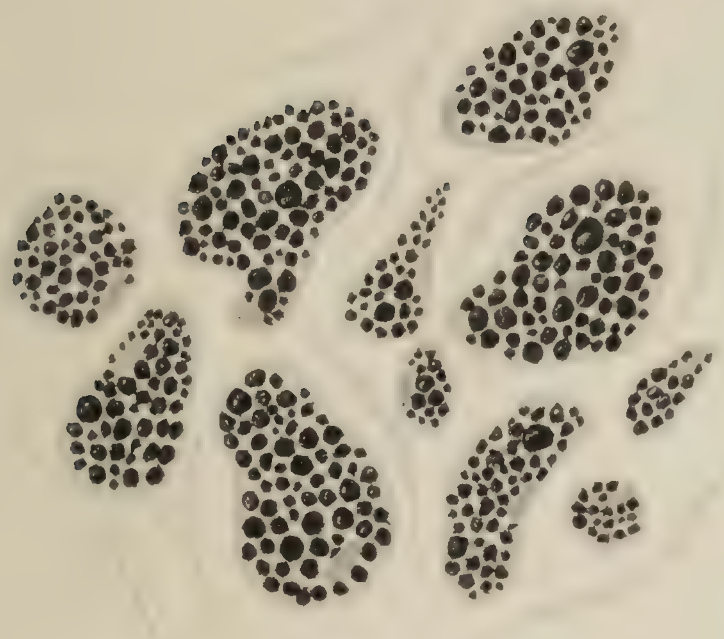
DESCRIPTION OF PLATE III.

FIG. 1. — Large lutein or endothelial-like cells in the intima heavily loaded with fat.

FIG. 2. — Stellate connective tissue cells with fat deposits.

FIG. 3. — Spindle-shaped connective tissue cells of the intima containing much fat.

FIG. 4. — Fatty degeneration of the muscle cells in the musculo-elastic layer of the intima.



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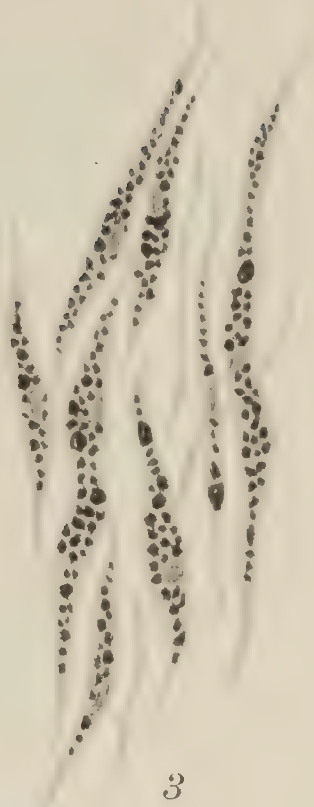

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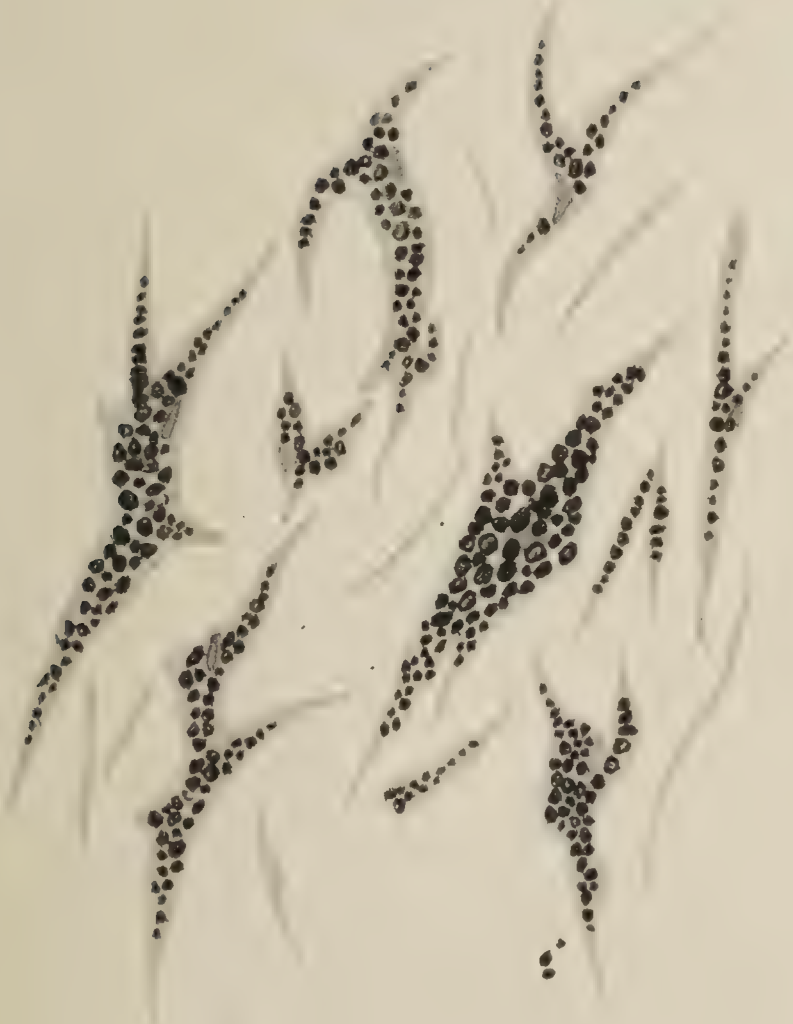

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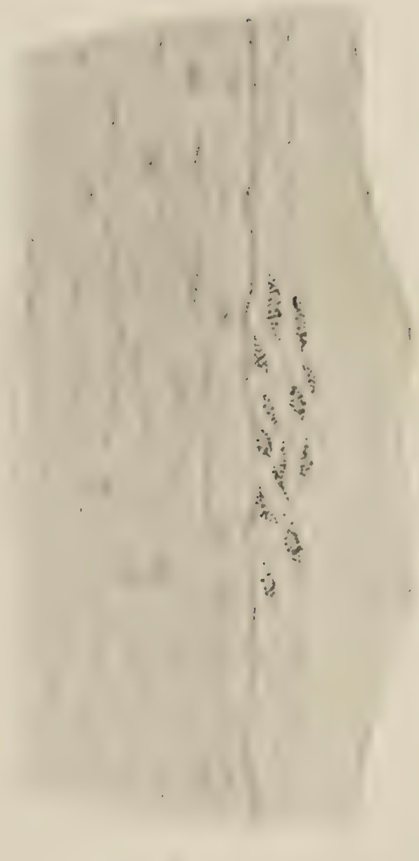

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Fatty degeneration

NODULAR ENDARTERITIS OF THE AORTA ABOUT THE INTERCOSTAL ARTERIES

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Reprinted from
The Journal of Medical Research, Volume XXXI., No. 3
(New Series, Vol. XXVI., No. 3), pp. 409-430, January, 1915

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Endarteritis is one of the most prominent and widespread reactions of the arterial tree. It is found in arteries of all sizes, and it is mainly through it that circulatory disturbances (referable to arterial disease) in different viscera are brought about. The variety of types of this disease have been repeatedly indicated (Virchow, Thoma, Friedemann, Jores, Chiari, Buerger), and although the disease process has been classified according to its gross character (diffuse, nodular, obliterating, thrombosing), this classification only takes cognizance of the fully developed lesion, when such changes as may readily be observed by the naked eye are recognized.

In endarteritis we must recognize a reaction which is very commonly seen on the intimal surface of the arteries, under most varied conditions. Not only have types of endarteritis been found associated with different systemic diseases (nephritis, Friedemann; lues, Heubner; acute infections, Simnitsky), but it is a very frequent accompaniment of a variety of other reactions in the arteries themselves. In known inflammatory processes of the arterial wall, particularly in syphilis, as well as in periarterial tuberculosis, an endarteritis is the rule, while an endarteritic process overlying an area of fatty degeneration in the deep intima is also common. On the other hand, small plaques of chronic endarteritis may appear in a vessel without evidence of a periarterial or medial inflammation and in the absence of any processes of degeneration in the deep intima which could be suggested as the causative factor in stimulating the overgrowth of the superficial layers. Recognizing, therefore, that the overgrowth of the superficial intimal tissues may be a response to irritants of different kinds, it was determined to study a series of vessels in the

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* Received for publication Sept. 24, 1914.

earliest stages of the process, as well as to collect observations upon the possible presence of reaction in a variety of infectious diseases, where naked eye lesions were not to be found. For the latter, studies were particularly carried out upon arteries of young individuals (ten to eighteen) who had just died of an acute infection (pneumonia, infective endocarditis, peritonitis, typhoid fever). The tissue for study which was selected was the aorta in the vicinity of the intercostal arteries. Moreover, similar studies were made upon individuals of more advanced years (thirty to sixty) who likewise had died of an acute infection. Here it was desired to observe the reaction, if any, which developed in or upon preëxisting nodular areas of the intima.

The presence of button-like areas of chronic endarteritis about the mouths of the intercostal arteries has been commented upon frequently. Similar isolated areas of endarteritis are observed about the mouths of other vessels branching from the aorta, but in frequency of distribution the descending thoracic aorta shows the nodular endarteritic thickening more commonly than the remaining portions of the central vessels. Their position upon the posterior wall and particularly about the intercostal arteries is characteristic, but difficult of explanation. For the distribution, particularly when it is recognized that their position is along the best supported portion of the aorta, the mechanical theory alone is wholly inadequate. That the intimal reaction is not in reponse to a medial weakening we hope to demonstrate in the subsequent discussion. And further, that we are not dealing with a process of response to simple "wear and tear" will, we believe, also be evident from this study.

We wish it to be clearly understood that the study here detailed deals with cases of infection and the cases have been selected on that account. We do not wish to have our conclusions misinterpreted as meaning to indicate that all processes of endarteritis have this origin, but rather to demonstrate that endarteritis may have an infectious origin, in which an inflammatory reaction, having a course not unlike that in other tissues and accompanied by fatty and other degeneration, may be observed. Here again it may be well to indicate that the mode of origin or the previous course of a fully developed plaque of endarteritis cannot be determined by a study of the old lesions alone, and it is futile to hold controversy over such an indeterminable problem. A study of the earliest stages of the lesions in the tissues of man is still the most secure upon which to base conclusions. Animal experiments in our own hands have given inconstant results, though an endarteritis has been produced in very young rabbits by the inoculation of B. typhosus, streptococci, and staphylococci (Crog, Klotz, Saltykow). Hence when in young individuals, tissue reactions in the arteries may be demonstrated in association with a definite systemic disease and infection, and the ear-marks of these reactions are comparable to the known reactions of these bacteria in other tissues, we are justified in indicating a direct or indirect relation between the vascular lesions and the systemic disease.

Whether the lesions discussed in this paper are to be spoken of as arteriosclerosis may not find universal agreement, and is dependent upon the interpretation by the many observers of the nature of the arteriosclerotic process. For my own part (as well as Marchand, Faber and others) the term arteriosclerosis is generic, not defining any one particular disease, but a process induced by a variety of factors whose end-result is a hardening of the arteries. I would, however, point out that although inflammatory reactions induced by bacterial irritants are, for the most part, of a productive (so-called regenerative) kind, they are commonly accompanied by degenerative processes. Fatty degeneration is prone to follow the various chronic productive lesions of the intima, where, by the very nature of the normal structure, a disturbance by thickening of its surface layer leads to nutritional depression. In luetic arterial lesions this degenerative reaction, even though the intima is much thickened, is often lacking, as the nutritional disturbance by the thickening of the inner coat is compensated by the extensive development of new vessels from the vasa vasorum.

It is to be remembered also that degenerative changes of the intima develop not only as a result of nutritional disturbances, but also through the action of noxious agents directly upon tissues and cells. It has been amply demonstrated that a variety of tissues and cells of the intima become involved in fatty degeneration, the sum total of which make up the areas of atheroma visible to the naked eye.

The materials studied comprised a series of twenty cases, ranging in age from ten to fifty-six years. The cases were selected with particular reference to the presence of a systemic infectious disease. In many of these bacteria were demonstrated during life by blood culture or at autopsy from the heart, peritoneum or lung. Control observations were made upon tissues obtained from a number of non-infectious cases.

Case.	Sex and Age.	Cause of Death.	Infection.
1	M. 10	Scarlet fever and otitis media.	
2	M. 11	Scarlet fever and suppurative angina.	
3	F. 13	Acute verrucose M. endocarditis (chorea).	Strept. salivarius.
4	F. 13	Appendicitis.	
5	F. 15	Acute verrucose M. and A. endocarditis.	Strept. fecalis.
6	M. 17	Acute verrucose M. endocarditis.	Strept. salivarius.
7	F. 18	Acute lobar pneumonia.	Pneumococcus.
8	M. 20	Appendicitis.	
9	F. 23	Typhoid fever and peritonitis.	B. typhosus; strept. pyog.; B. coli.
10	M. 25	Typhoid fever.	B. typhosus.
11	M. 26	Recurrent M. and A. endocarditis.	Strept. mitis.
12	M. 28	Typhoid fever.	B. typhosus.
13	M. 29	Appendicitis.	
14	M. 30	Acute lobar pneumonia.	Pneumococcus.
15	F. 33	Typhoid fever.	B. typhosus.
16	M. 34	Acute lobar pneumonia.	Pneumococcus.
17	M. 39	Acute dysentery with peritonitis.	B. dysenteriæ (Flexner varians); B. coli.
18	F. 48	Acute lobar pneumonia.	
19	M. 55	" " "	Pneumococcus.
20	M. 56	Strangulated hernia and peritonitis.	Strept. pyog.; B. coli; Staph. aureus.

Sections were cut of the aorta in the neighborhood of the intercostal vessels. These sections were made by cutting the blocks (paraffin) in different planes, transverse, longitudinal, and on the flat. An opportunity is thus given to study the disposition and grouping of cells, which cannot be obtained by a study of one set alone. Particularly valuable were the sections cut and mounted serially, which were obtained by cutting on the flat, beginning with the intima and ending in the adventitia. These blocks were taken so as to leave an intercostal artery in the center. By observing the tissues about the mouths of the intercostal vessels, and following the reactions in the vessel as it passed through the aorta, a good picture could be gained to indicate the nature of the process which terminates in nodular endarteritis. These sections made from flat portions of the aorta demonstrate an entirely new character to the deposition of the elements in the arterial wall. The arrangement of the cells in each succeeding layer is well brought out, while any alteration from the normal character or the presence of foreign cell elements is the more striking and quickly recognized.

The alternate sections of the paraffin blocks of each series were stained with hematoxylin and eosin, and by Verhoeff's method for elastic tissues. At the same time frozen sections were also made from adjoining areas of the vessel wall and stained with Sudan III. and hematoxylin, and a double stain of Sudan III. and Verhoeff's. The frozen sections of the aorta on the flat, stained by Sudan and hematoxylin were unusually instructive. The disposition of and the elements involved in the process of fatty degeneration were readily recognized.

The intercostal arteries are not individual and self-contained structures until the outer border of the aorta is reached. At their mouths on the inner surface of the aorta their boundary consists only of the intima of the aorta which dips downward and continues as the intimal lining of the efferent vessel. The internal elastic lamina of the aorta is also continuous with the innermost elastic layer of the intercostal vessel. Other than this, a thin intimal structure with an outer elastic zone, the intercostal artery possesses no elements of its own during its passage through the inner two-thirds of the aorta. In the outer part of the aorta the perforating artery gradually takes form, and elements from the wall of the aorta enter into an orderly arrangement imitating a small vessel of the elastic type. The internal elastic lamina becomes more marked, and the media is well supplied with concentrically arranged elastic fibers. Moreover, in the outer part of the aorta, and while still within the media, the perforating intercostal vessel shows a fibrous tissue adventitia in which lymphatics and small blood vessels may be demonstrated. Thus the point of exit of each intercostal artery has a fibrous tissue mass which continues to surround the artery in the outer third of the aortic media. This connective tissue invasion of the aorta simulates that seen about the vasa vasorum, with this difference that the intercostals as they pass through the outer part of the aorta are provided with their own vasa vasorum.

The elastic elements entering into the structure of the efferent vessel vary in their arrangement from the inner surface of the aorta until the artery emerges from the adventitia. The elastic elements of the deep layer of the aorta are continued into the intercostal branches forming a definite boundary separating the elements of the media of the aorta from the intimal tissues of the branches. At times, this inner elastic boundary is sharp and definite, forming an elastic ring as is found in the peripheral arteries. At other times again the inner elastic lamina is an ill-defined layer which does not differ from the elastic elements which surround it on the outer side, and which are essential elements of the media of the aorta. It is observed, however, that as the branching artery passes through the aortic wall the elastic bands take a more definite arrangement to the efferent artery, and become disassociated from the elastic fibers in the media of the aorta. Moreover, in the outer part of the aorta the perforating vessel possesses a definite internal elastic lamina of its own simulating more the arrangement of this tissue in the peripheral vessels.

During the passage of the intercostal arteries through the wall of the aorta they do not possess a true media. The tissues which support the small artery belong to the aorta. The muscle and elastic elements of the media separate at different angles leaving an oval opening but which, on account of the many directions of the spaces, form a central circular lumen. From these neighboring tissues a number of fibers are given off which enter into the composition of a more or less circular structure, the intimate wall of the efferent artery. In the outer third of the aorta this arrangement becomes more and more a part of the new vessel, until at the point of exit the artery possesses its regular layers. The character of the new vessel is that of the arteries of the elastic type where the media is richly supplied with elastic fibers. However, these elastic elements do not maintain a parallel arrangement to each other as do those in the media of the aorta. At a little distance from the aorta the elastic fibers gradually diminish in number until the media contains only sparse and branched elements as are present in other peripheral arteries.

In a like manner the muscle cells within the wall of the branching artery are but elements derived from the parent vessel. Their course lies parallel with the elastic fibers, some simply diverging from their usual direction to permit the efferent vessel to pass, others taking a somewhat circular course about the perforating lumen. Muscle cells were not noted in connection with the deep layer of the intima.

The intima of the intercostal branches as they lie in the wall of the aorta appeared very simple. An inner endothelial layer lies upon a narrow strip of connective tissue. No other elements than fibrous tissue were observed in this subendothelial coat. The indefinite inner elastic lamina marked the outer bounding of the intima and separated it from the tissues of the media of the aorta. As noted before a true media distinguishable from the tissues of the media of the aorta does not exist for these efferent arteries during their course through the wall of the aorta.

Recently Yamagiwa and Ito have shown that the mouths of the intercostal arteries are each provided with a valve-like lip which projects downwards from the upper border. Such a projection would tend to develop unusual currents about the openings of these vessels and possibly lead to small whirlpools under the projecting margin. It is claimed that some of these thickened borders contain muscle bundles. We have been unable to demonstrate them.

Thus the exit of the intercostal, as well as the small intervertebral arteries, differs materially in its architecture from that of the large vessels of the arch. The character of the opening on the surface of the aorta, no doubt, gives rise to a different blood current than at the mouths of the larger vessels where a more or less steady stream constantly rushes through. To measure and examine the character of these currents is not possible, and a mathematical determination, dependent upon the size of the lumen of the vessel, is not justified by fact. It is not probable that the different character of the blood stream over the surface of the arteries is alone sufficient to stimulate histological changes in the intima, but it may have a bearing upon the localization of bacteria or the influence of their toxins upon the underlying tissues.

The character of the reactions observed in the walls of the arteries of the cases studied showed a considerable variation. Most instructive were the vessels of the younger individuals where no evidence of a previous reaction or disease was present. In the arteries of older individuals care must be exercised in separating the tissue changes which may be of recent date from those of longer standing and different causes. Attention must, moreover, be paid to all portions of the arterial wall, noting the reactions in the adventitia and media as well as the intima. As we have previously pointed out, an inflammatory infiltration is not uncommonly present about the vasa vasorum, and in our study upon the arterial lesions of acute rheumatic fever particular stress was laid upon this, because of the possible sequelæ of acute destructive mesarteritis or of chronic interstitial mesarteritis. In our former study the slight lesions observed in the intima were not further studied, it being indicated, however, that some reaction of infiltration by wandering cells and proliferation of the connective tissues was evident.

In our present observations the consecutive changes have been followed, to indicate the process whereby the mild and early change in the intima gradually assumes the characters so commonly described as chronic endarteritis. In whatever manner the active factor of the systemic disease may act, whether by the bacteria, their toxins or through disturbed metabolism, will not at present be further discussed. We can only indicate that an irritant is present, whose response is a tissue reaction, infiltrative, proliferative, and degenerative.

The earliest response we have observed in the intima is a loosening of the narrow connective layer, simulating an edema. The change may be very slight, but sufficient, nevertheless, to show that the thickness of the tissues on the inner side of the internal elastic lamina (of both central and peripheral vessels) is not uniform. The connective tissue fibers show a fine loose meshwork with clear spaces. Occasional cells of a lymphocyte type are also present, but every evidence of a fatty degeneration is wanting. The internal elastic lamina is usually uninvolved, showing neither splitting nor degeneration. At other times this elastic layer appears granular along its inner border and does not stain uniformly opposite the point of subendothelial thickening. These mild reactions are readily overlooked. The media is uninvolved, save where an occasional vasa vasorum shows a mild edema or collection of a few lymphocytes and plasma cells.

The stellate connective tissue cells of the intima are best seen in the sections cut on the flat. Here they show a meshwork with fairly wide spaces, looking not unlike the fibrous tissue cells of cultures in vitro as have been described by Burrows, Weil, Lambert and Hanes and others. The wandering cells are most frequently found near the surface while few are seen, in the early stages, at the inner border of the media. At this period, too, there is a comparable reaction about the vasa vasorum. This, as we have on a former occasion described, begins in a loosening of the stroma about these small vessels in the adventitia and media, and accompanied by a few lymphocytes and occasional plasma cells and leucocytes. It is to be recognized that normally a few lymphocytes are found about some of these vasa in the adventitia, but their uniform presence about the majority of nutrient vessels, as well as their occurrence with plasma cells and leucocytes in the outer portion of the media, must be appreciated as distinctly pathological, and in the light of an inflammatory reaction.

In the early stages, the reactions are isolated to the tissues of the intima and those immediately surrounding the vasa vasorum. No changes are to be observed in the inner portion of the media, so that an uninvolved tissue is found to lie between the reactions in the inner and outer portions of the vessel wall. It would thus appear that the early reactions in the intima and about the vasa vasorum are unassociated.

The intensity of the reaction in the intima is not uniform, but is distributed in irregular microscopic patches over the surface. In the aorta these areas are more frequent about the mouths of the efferent vessels, and are particularly frequent at the points of exit of the intercostal arteries. They are frequent just at the ridge over the mouth of the vessel, and commonly extend inwards for some little distance along the lumen of the intercostal branch. These plaques, however, become less frequent in the intima of the intercostal, as this vessel perforates the deep portion of the aorta and passes beyond its confines.

As the process advances the tissue changes become more marked. This is mainly observed in the greater infiltration of cells, lymphocytes, some leucocytes, and a few plasma cells. The greater number of cells are still observed near the surface, although the infiltration now occupies the entire depth of the intima and to some extent the neighboring border of the media. This infiltration is fairly diffuse in the involved plaque, with, besides the more marked aggregation at the surface, occasional groups of cells in the meshes of the connective tissue. Where these groups are found there may also be observed the presence of large mononuclear cells, with vacuolated protoplasm bearing a resemblance to the lutein type of endothelial cells. These large mononuclears lie in groups in the connective tissue of the intima, and in the early plaques are best seen in sections cut on the flat. With the appearance of these large mononuclears, degenerative changes may be observed. These cells in themselves contain much fat-staining material, and even though the cells are loaded with fat granules, the nucleus remains centrally placed. Free fat is not seen in any part of the intima and no evidence is at hand to indicate that the fat is deposited by a mechanical process as was suggested by Ribbert and Aschoff. On the other hand, other degenerative processes are also occurring in the tissues. The connective tissue fibers are no longer as distinct, but are aggregated in masses of matted fibrils which appear swollen and indistinct. A hyaline appearance is overshadowing the fibrous tissue structure. Fat may also be demonstrated in some of the connective tissue cells, forming wedges of deposit at the ends of the nuclei. Here and there, the elastic bands of the deep layer of the intima have lost their typical staining and are found to contain a fatty material which stains diffusely in the swollen bands.

Other than a somewhat more marked cellular infiltration about the vasa vasorum and the presence of a few wandering cells at the inner border, the media shows little evidence of further change. Evidence of degeneration is only present in the muscle cells and the elastic fibers of the media in the immediate vicinity of the vasa vasorum.

With the development of early fatty degeneration in the intima there is observed a change in the elastic elements in the outer portions of the intima. In the aorta and still better seen in the larger peripheral vessels the internal elastic lamina undergoes splitting. The elastic lamina becomes granular and may even show the presence of fat in the areas of degeneration, while the muscle fibers on its inner side appear more prominent through the presence of fine fat droplets within them. In our preparations the splitting of the elastic lamina and the early development of a fatty degeneration in the cells of the immediate vicinity, though appearing a little later than the first changes in the inner connective tissue layer, are a progressive accompaniment of the inflammatory process. The development of fine elastic fibrils, in the intermediate zone between the intima and the media and which extend later into each of these layers, is also an early reaction in these lesions.

In the later stages of the systemic disease much of the reaction, particularly the edematous swelling of the intima and the cellular infiltration, may disappear. This is particularly evident in the disappearance of the visible intimal change after typhoid fever. Almost complete restitution of the tissues results. Even much of the products of degeneration is removed so that neither fatty deposits nor hyaline change can be recognized on the posterior wall of the aorta where they are prone to occur. On the other hand, even where naked eye evidence of perfect repair presents itself, some permanent alteration of the tissues of the intima may be recognized microscopically. The superficial layer of connective tissue of the intima is slightly increased in amount forming a thin laminated structure parallel to the surface. An increase in very fine fibrils of elastic tissue is also evident in the intima as well as in the inner media adjacent. Furthermore, the not uncommon splitting of the inner elastic lamina remains as a permanent alteration, though the accumulation of fat granules in the different types of cells may, to some extent, disappear.

The presence of new connective tissue in the intima becomes definite with the progress of the lesions, and in some specimens it would appear that a certain amount of hyperplasia of the subendothelial layer continues even after all evidence of the acute stage has disappeared. The reaction which takes place is a process lying entirely within the intima and does not result as the organization of an exudate upon the inner lining of the artery. Moreover, although wandering cells, chiefly of the lymphocytic variety, constitute the early reaction, a true process of interstitial organization is not the mode of repair in the intima. We have not observed the presence of capillaries in this structure, nor any attempt on the part of the vasa vasorum to send branches towards the lesion in the intima. The tissue changes are progressive and the connective tissue cells take part directly by proliferation.

At the withdrawal of the wandering cells, the new connective tissue establishes itself as a permanent mass of new fibers forming a greater or less thickening of the coat.

In the specimens of older individuals, evidence was at hand of a former connective tissue thickening of the intima. These were accompanied by tissue changes of degeneration as are commonly observed in chronic endarteritis. In some, the deep fatty change was evident to the naked eye, while the connective tissue hyperplasia formed a hyaline pearly plaque over it. Moreover, the various types of change in the musculo-elastic layer were recognized in many. In such specimens it is impossible to say in what manner the old endarteritic process was brought about. Was it primarily the result of an inflammatory reaction as we have indicated in the above observations, or did it develop only as a connective tissue hyperplasia, secondary to the fatty deposit in the deep layer? That the latter type of reaction does occur in the intima we feel fully convinced and have previously discussed elsewhere.

However, in the present series we have observed that the areas of old connective tissue thickening of the intima may become the seat of new and more acute reactions. An infiltration by wandering cells begins from the surface and extends into the superficial connective tissue which has again become quite loose. The reaction may remain quite superficial or may advance deeper into the old connective tissue plaque. The area of fatty degeneration in the base of the lesion may show the presence of a lymphocytic infiltration in the surrounding stroma. It is, however, of particular interest to observe the reactions which take place in the upper layer of the intima, where the progressive changes simulate those previously noted in younger individuals. The infiltration by cells, though mainly lymphocytic, also contains plasma cells and occasional leucocytes. Passing through stages of edema and infiltration it can finally be seen that a new increase of connective tissue has taken place. This new hyperplastic layer lies as a cap over the former compact and hyaline connective tissue area of the intima. Thus old lesions may become the site of new attacks of endarteritis.

It has been repeatedly indicated and more particularly discussed by Jores and later by Aschoff that the amount of the superficial connective tissue layer is not constant, and that at different ages a considerable variation may be noted. Thoma laid particular stress on the progressive increase of this connective tissue in the " nabelblutbahn," which may be looked on as a physiological process. Subsequently others have found that this connective tissue growth is not isolated to the " nabelblutbahn " system but may be seen in varying degree in other arteries. Moreover, Jores has pointed out that a sharp demarcation of this physiological growth of connective tissue cannot be made from the early pathological processes of this subendothelial layer. He does, however, insist that when the growth of connective tissues not alone involves the superficial layer but also spreads into the deep musculo-elastic layer, the process is always a pathological one.

The presence of the physiological connective tissue increase is not accompanied by degenerative changes, but when hyaline change is observed in the superficial layer or fatty degeneration is present in the deep portion of the intima, a simple process of tissue growth is not to be thought of. We would, however, indicate that all forms of fatty degeneration found in the intima in association with a connective tissue overgrowth are not a common process. As Jores has shown, a mixed type of hyperplasia of the musculo-elastic layer showing fatty degeneration with a superimposed connective tissue " regeneration " is not uncommonly noted. Furthermore, however, fatty degeneration may accompany the process of connective tissue growth of the intima without any involvement of the musculo-elastic layer. These degenerative changes are found in the connective tissue cells and in the large endothelial-like cells, which aggregate in small groups in the tissues of the inner layer of the intima. The presence of fatty deposits within the elastic fibers of the intima has also been observed in the absence of proliferative changes in the musculo-elastic layer.

Jores has restricted the term arteriosclerosis to the one type of intimal change in which an hyperplasia of the musculo-elastic layer and a splitting of the internal elastic lamina is accompanied by fatty degeneration of the longitudinal muscle fibers. Where a superficial thickening of the connective tissues occurs over this process it is viewed by him as always secondary. Furthermore, the fatty degeneration which develops in the layer of connective tissue thickening is viewed as secondary to degenerative processes in the deep musculo-elastic layer. From our observations this does not always appear to be the case. We have repeatedly seen proliferative changes in the superficial connective tissue without involvement of the musculo-elastic layer, in which the newly developed tissue showed fatty deposits in the connective tissue cells as well as showed the presence of cells apparently foreign to the intima, the large lutein-like cells, which were loaded with fat. Under the Virchow classification, this would constitute a simple fatty degeneration of the intima, a passive process as opposed to atheroma which develops in the deepest part of the intima and is viewed as an active process. We must agree that in this stage of fatty degeneration when the fat is still contained within living cells the term atheroma is inapplicable, and it is even more than probable that many of these cells containing fat may recover their normal function with the disappearance of much fat from the tissues. On the other hand, a continuation of the deleterious influences upon the vessel wall must bring about destruction of the involved cells with the deposition of free fat in the tissues. Such deposits must be viewed as atheroma. Furthermore, the presence of these masses of free fat may further stimulate, as is suggested by Jores, Faber and others, the further proliferation of connective tissue in its vicinity.

I would draw particular attention to the presence of the large endothelial-like cells (lutein-like cells) which occur in the connective tissue layer of the intima under conditions of proliferation. Much has been said by recent observers concerning the presence of these cells in the vessels of experimental animals fed with cholesterin and lipoids. In fresh preparations doubly refractile lipoid bodies (cholesterin-esters) have been demonstrated within these cells

(Anitschkow). Similar cells may commonly be demonstrated in human arteries where the fatty degeneration occurs in the superficial layers of the intima, and when such specimens are cut (frozen) on the flat, they are seen as compact aggregations in which the lipoid substance is almost entirely intracellular. That this type of fatty degeneration of the intima forms an important factor in the subsequent development of atheroma, even in the absence of hyperplasia and degeneration of the muscle layer of the intima, appears obvious.

Rokitansky was among the first to view the nodular thickening of the arteries in the light of a pseudo-inflammatory process, although he did not believe that the intima itself, being a nonvascular tissue, was capable of undergoing true inflammation. The intimal plaques, he believed, were the result of a blood deposit upon the surface, which subsequently became converted into a tissue mass by cells derived from the blood. Others soon opposed this view, Engel, Crisp, and Naumann each finding that the intima was capable of an inflammatory process. Particularly, however, was Rokitansky's attitude attacked by Virchow, who not only demonstrated that the intima, like other nonvascular tissues, may be the seat of inflammation, but that a proliferation of its own cells leads to the nodular masses on the surface. He compared nodular endarteritis with chronic endocarditis where an inflammatory thickening results mainly in connective tissue proliferation without an extensive cellular infiltration. Cohnheim, Engelhardt and others also accepted this view, differing, however, in minor points respecting the origin of the leucocytic infiltration. Traube found that the white cells, infiltrating the intima, were derived directly from the blood stream, while Friedlander and Koester believed their origin to be from the vasa vasorum. Koester's findings are particularly interesting in that he noted the simultaneous cellular infiltration about the vasa vasorum and in the intima. His descriptions even indicate that under inflammatory conditions the capillaries of the media extend closer to the intima, and a rich lymphatic system extends from the media to the intima. While the acute inflammatory processes were accompanied by a round cell infiltration, he observed that a connective tissue proliferation was present both in the intima and about the vasa vasorum in the chronic stages.

Our own findings have led to conclusions which, to some extent, are similar to those of Koester. The simultaneous presence of a small cell infiltration in the vicinity of the vasa vasorum and the intima may be observed during the acute stages, but we have not been able to demonstrate a constant relation between them in the arterial wall. The localization of one or the other in the artery is not always accompanied by a similar reaction in the other arterial coat opposite to it. In other words, though an inflammatory reaction may be demonstrated about the vasa vasorum in the adventitia and outer portion of the media, a similar process may not lie opposite to this in the intima. Moreover, where the simultaneous presence of a cellular infiltration has been observed in the inner and outer coats of the artery, there has always appeared a strip of media adjacent to the intima which was uninvolved in the inflammatory process. It would, therefore, appear that these reactions are individual, though frequently occurring side-by-side in the same vessel. The cellular exudate found in the intima appears to arise by a direct migration of the wandering cells from the surface of the artery.

Wiesel has made some interesting observations upon the arterial system of individuals under twenty-four years of age who had suffered an acute infection (scarlet fever, pyemia, diphtheria, typhoid fever, pneumonia). A variety of reactions of an inflammatory nature along with degeneration of the muscle cells and the elastic fibers was noted. He suggested the name "arteritis chronica postinfectiosa" for this condition which he believed was not related to arteriosclerosis. Faber also observed a variety of degenerations in the aorta after acute infections, and he suggested that the injury to the media, "dilatation, hypertrophy and hyperplasia of the entire vessel wall might occur." Hansen had recorded similar findings, but, going even further, stated that the acute infections had a direct influence upon the development of atheroma.

In Prag, Simnitsky also had his attention attracted to the presence of intimal thickening, degeneration (fatty), splitting of elastic fibers, in the aorta of young persons who had died of acute infections.

Although inflammatory reactions have been observed in the inner part of the intima under a variety of infectious diseases, the outcome of the process is not the same in all cases. Gradations of intensity of the primary inflammatory process may be observed in the early stages, while the nature of the repair in the older lesions also varies. As we have indicated, it is probable that many of the milder reactions, seen in the acute stage, may disappear without leaving recognizable change, but it is impossible to indicate from the appearance of a given lesion the subsequent outcome of the process in the arterial wall. Inflammatory reactions of the intima of longer duration are always accompanied by a connective tissue disturbance of a proliferative kind, and from them there develop the intimal thickenings of the "hyaline" type. These reactions are frequently of the pure connective tissue variety, but are sometimes associated with hyperplasia of the muscle layer of the intima and splitting of the elastic lamina. Nevertheless, the splitting of the elastic lamina cannot alone be taken as an indication of a hyperplasia of the deep muscle layer, as we have seen it in pure regenerative processes of the inner coat where no proliferative response was seen in the muscle tissue of the intima.

It is obvious that with the degree of the reaction in the intima, the component tissues will take part in bringing about a structural alteration in the involved area, at times proliferative, at others degenerative in kind. When, however, the harmful influences (particularly bacterial toxins) are so great, the proliferative changes give way to processes of degeneration of which the fatty is most easily demonstrated, and which may be recognized in a variety of tissues and cells. Whether all well defined processes of fatty degeneration of the intima shall be called atheroma finds no common agreement. For my own part, when the fatty degeneration of the intima has proceeded to that stage, that not alone do we find fatty substances within the cells, but also that some of it has been liberated, by the death of cells, into the interstices of the tissue, giving rise to a free greasy deposit, do I speak of it as atheroma. Other products of degeneration, particularly the calcareous, are also mixed with the atheromatous deposit. From our observations it is clear that this atheromatous material may arise not only from the destruction of one type of tissue (deep intimal muscle), but also from degenerative changes in the elastic fibers, connective tissue, and the endothelial-like (lutein-like) cells.

CONCLUSIONS.

It would appear from the present study that contrary to our opinion previously expressed, the reactions in the intima, in many acute infectious diseases, may occur independently though simultaneously with the inflammatory reactions about the vasa vasorum.

The intimal reactions of the aorta are more marked about the mouths of the smaller vessels, particularly the intercostals, but they do not usually advance along the lumen of the branching vessel.

The reaction is an inflammatory one, in which the infiltration of wandering cells (lymphocytes and some plasma cells and polynuclear leucocytes) may best be observed when the tissues of the intima are cut on the flat.

The inflammatory process is accompanied by progressive as well as degenerative changes in the tissues of the intima. Repair is accomplished by a proliferation of the connective tissues of the inner layer of the intima and may show some hyperplasia of the musculo-elastic layer.

Splitting of the internal elastic lamina into multiple bands occurs in reactions of a purely inflammatory nature in the absence of hyperplasia of the deep muscle layer.

Fatty degeneration is a common accompaniment of the pure connective tissue thickening of the intima, and is found to involve particularly the connective tissue cells, the elastic fibers, and the endothelial-like cells found in the intima.

Deep areas of degeneration also show the involvement of the muscle cells of the intima.

The late stages of the lesion cannot be differentiated from processes of atheroma with superficial endarteritic thickening. It is superfluous to differentiate atheromatous softening of the intima by the particular tissue cells which show fatty degeneration and which on subsequent destruction liberate fatty materials in the intima of arteries.

It is probable that the structural changes brought about in the intima of the arteries in infectious diseases are the result of bacterial toxins, but it is possible that a vicious circle is set up in the affected area by which nutritional alteration and decomposition products of tissues also exert an influence upon the surrounding parts.

The entire process must be classed as one of arteriosclerosis in which proliferative and degenerative reactions are closely associated.

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The Journal of Medical Research, Vol. XXXI., No. 3, January, 1915.

Reprinted from the Transactions of the Association of American Physicians, 1914

EXPERIMENTAL BACTERIAL INTERSTITIAL NEPHRITIS

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The presence of kidney lesions in individuals suffering acute intoxications and infections, is universally recognized, but the relation of these acute disturbances to subsequent and permanent renal damage still offers great difficulty to the clinician and pathologist. That the kidneys should respond to many varieties of intoxication is obvious, and that the response may, at times, be within the bounds of its physiological activity, at other times overstep this limit and be pathological, is also evident. Where the dividing line between the physiological and the pathological processes falls is hard to indicate, save where we set a normal objective standard for the clinician and pathologist. For the clinician this had been done by Richard Bright (1828). For the pathologist many have been indicated (Rayer, Reinhart, Frerichs, Wilkes, Ribbert, Weigert, and others), and recently Vollhart and Fahr have set forth a new classification, which means to correlate the clinical and pathological findings for a fuller understanding.

A common agreement has been reached in recognizing two distinct types of changes in the diseased kidney, the regressive or degenerative and the progressive or proliferative. Each of these may appear in the absence of the other, but not uncommonly they occur together, appearing either simultaneously or one of them may be primary. Difficult it is, however, to determine what part each of the tissue reactions has played in bringing about the manifestations noted during life, and the relation of the cellular changes to each other needs further investigation. Whether, as Aschoff has indicated, the inflammatory process is much more comprehensive in kidney diseases than is accepted by most, appears to rest upon the individual views of the inflammatory process. Whether cloudy swelling and its sequel is viewed in the light of inflammation is an issue of significance not isolated to the kidney.

It is of interest to note that not a few of the studies upon true nephritis of one kind or another have been made upon the kidneys of infectious cases in which the heart was concurrently involved. These studies have been particularly interesting in demonstrating a variety of lesions (in all stages of the disease), in which tubular and glomerular degenerations were demonstrated. Moreover, microscopic embolic lesions of the glomeruli have recently received much attention (Gaskell, Baehr). In many of the studies upon human material, individual authors have laid particular stress upon one or another finding as indicating the significant process of the kidney in the disease. When, however, we correlate these pathological observations, a rather complex reaction is found to be present. In other words, so various may be the exciting cause in its effect upon the kidney structure that though a dominant character may be outstanding, a complicated involvement of different structures changes the general appearance. It is also evident that such a sensitive organ as the kidney will respond not only to the initial agent of the disease, but as sytemic derangements occur, will also show the effects of these.

Experimental kidney lesions have been induced by a variety of chemical agents, the salts of mercury, uranium and copper being chiefly studied. Organic compounds (tartrates and acetates), alkaloids (cantharadin, aloin), and venoms have also been found effective in bringing about severe renal disturbances. In the main, these lesions have consisted in degenerative processes affecting the secretory cells, but some have also observed the presence of interstitial inflammatory reactions, as well as vascular and glomerular lesions. The point here to be noted is that many soluble chemical bodies brought to the kidney by the circulation act upon that portion of the kidney structure which deals with them in the process of excretion, and the damage of the renal structure is, for the most part, observed in the parenchymatous cells as a degeneration, varying from a mild granular and edematous change of the protoplasm to the more serious nuclear disturbances and complete death of the cells. However, alterations are also observed in the interstitial tissues, glomeruli, and bloodvessels, where an edema, proliferation of connective tissues, or a mild inflammation with cellular exudate is not uncommon. We mention these combinations of reactions merely to indicate the complexity of the reactions which also attend the experimental lesions, where a single agent has been used.

The frequency of kidney disease associated with infective heart lesions led us to isolate, from a series of primary or recurrent cardiac disease, the organisms, obtaining them either during life in blood cultures or from the heart blood at autopsy. These organisms all belong to the group of streptococcus viridans (Schotmüller), and by cultural means have been classified by my colleague, Dr. W. L. Holman. From cases of infective endocarditis we have isolated the Streptococcus salivarius, Streptococcus fecalis, Streptococcus mitis, and Streptococcus equinus. These organisms as well as similar ones isolated from different sources (mouth, throat, intestine, feces) were used for the inoculation of animals. For the most part emulsions of a luxuriant growth on blood agar were inoculated into the ear vein of rabbits. Heavy growths in serum broth were also used in a few cases, but were discarded as bacterial clusters and precipitated albumen could not be avoided in the materials for inoculation. All of the cultures were relatively recently isolated, and some were used as soon as they could be grown on media and their purity demonstrated. In no instance did suppuration arise either at the point of inoculation or in the internal organs. In many animals repeated inoculations were made, as it was found that the organisms rapidly disappeared from the blood stream. It was found, however, that although the blood might be free from organisms these could be occasionally demonstrated in the internal tissues (spleen, kidney, liver, and lymph glands). After varying intervals the animals were killed or died. Tissues were then collected at autopsy and fixed in Zenker solution and formalin.

TABLE I

Case.	Number.	Culture.	Type of streptococcus.	Inoculation.	Total interval before death.	Death.
1	XVI	391.0	S. salivarius	June 7, 1913	2 days	Died
2	I	223.0	S. salivarius	Nov. 11, 1912	4 days	Died
3	XXXV	531.6	S. fecalis	Dec. 22, 1913 Dec. 26, 1913 Dec. 30, 1913	9 days	Died
4	XXXIX	520.0	S. salivarius	Dec. 22, 1913 Dec. 26, 1913 Dec. 30, 1913	11 days	Died
5	IX	260.0	S. mitis	May 19, 1913	15 days	Killed
6	X	339.0	S. equinus	May 20, 1913	15 days	Killed
7	XI	312.0	S. mitis	May 20, 1913	16 days	Killed
8	XXXVI	531.6	S. fecalis	Dec. 22, 1913 Dec. 26, 1913 Dec. 30, 1913 Jan. 3, 1914 Jan. 6, 1914	16 days	Died (pneumonia)
9	XXIV	372.2	S. viridans	June 23, 1913	20 days	Died
10	VIII	247.0	S. mitis	Dec. 3, 1912	31 days	Died
11	XXXVII	463.0	S. mitis	Dec. 22, 1913 Dec. 26. 1913 Dec. 30, 1913 Jan. 3, 1914 Jan. 6, 1914	31 days	Killed
12	XII	369.0	S. fecalis	June 4, 1913	33 days	Killed
13	XIII	371.2	S. viridans	June 4, 1913	33 days	Killed
14	XIV	371.4	S. mitis	June 4, 1913	33 days	Killed
15	XXIX	369.1	S. fecalis	Oct. 8, 1913 Oct. 24, 1913 Nov. 17, 1913	41 days	Killed
16	XVIII	212.0	S. fecalis	June 16, 1913	43 days	Killed
17	XIX	391.0	S. salivarius	June 16, 1913	45 days	Killed
18	XV	337.0	S. salivarius	Mar. 19, 1913 Apr. 4, 1913 Apr. 11, 1913 Apr. 24, 1913 May 3, 1913	47 days	Killed
19	XXIII	224.0	S. fecalis	June 24, 1913 Aug. 11, 1913	49 days	Died
20	XXVIII	391.0	S. salivarius	June 25, 1913 Aug. 11, 1913	49 days	Died
21	V	223.0	S. salivarius	Dec. 3, 1912 Jan. 24, 1913	52 days	Killed
22	XVII	260.2	S. fecalis	June 7, 1913	53 days	Killed
23	XXII	334.0	S. salivarius	June 24, 1913 Aug. 11, 1913	53 days	Killed
24	XXVI	369.0	S. fecalis	June 25, 1913 Aug. 3, 1913	53 days	Died (pneumonia)
25	III	223.0	S. salivarius	Nov. 16, 1913 Nov. 25, 1913	83 days	Killed
26	XXI	339.0	S. equinus	June 24, 1913 Sept. 19, 1913	105 days	Killed (cocidiosis)

Case.	Number.	Culture.	Type of streptococcus.	Inoculation.	Total interval before death.	Death.
27	XXV	385.0	S. mitis	June 25, 1913 Sept. 19, 1913	105 days	Killed
28	XX	210.5	S. viridans	June 16, 1913 Sept. 19, 1913	103 days	Killed
29	VII	212.0	S. fecalis	Dec. 3, 1912 Feb. 1, 1913	125 days	Killed
30	VI	224.0	S. fecalis	Dec. 3, 1912 Feb. 1, 1913	134 days	Killed
31	XXVII	210.3	S. viridans	June 25, 1913 Sept. 19, 1913 Oct. 13, 1913	148 days	Killed
32	XL	369.1	S. fecalis	Oct. 8, 1913 Oct. 24, 1913 Nov. 12, 1913	149 days	Died (pneumonia)
33	II	224.0	S. fecalis	Nov. 11, 1912 Nov. 15, 1912 Nov. 25, 1912 Feb. 1, 1913	163 days	Killed
34	IV	212.0	S. fecalis	Nov. 21, 1912 Nov. 25, 1912 Feb. 1, 1913	228 days	Killed
35	XXXV	Control	antihuman red-blood cells, amboceptor, rabbit			
36	XXXVI	Control	Normal (young animal)			
37	XXXVII	Control	Normal (full grown)			
38	XXXVIII	Control	Normal (full grown)			
39	XXXIX	Control	Normal (full grown)			
40	XL	Control	Normal (young animal)			

In all, 40 rabbits were used in the experiments, of which 6 served as controls. Of the remaining 34 which received treatment, 4 were excluded from consideration on account of other spontaneous disease, 3 having pneumonia, and 1 showing a coccidial infection of the liver. Some of the treated animals died shortly after the first or subsequent inoculations. In them the dose of organisms given was too great for the primary resistance of the individual animal. Other animals receiving the same amount of the same organisms withstood the infection without fatal results. A comparison of the tissues from animals dying at different intervals gave a good picture of the character of the reaction in its different stages. It was also noted that some animals receiving a single injection, and more particularly animals receiving repeated inoculations, became progressively emaciated and died at fairly long intervals after the last treatment. Such a progressive effect upon the animals is suggestive of a latent infection, or it may be of severe damage upon vital organs, which spontaneously become worse. The systemic derangements are not alone referable to the damage upon kidney substance, for in not a few are lesions also demonstrable in the heart muscle, endocardium, and vascular system. Concurrent organic lesions were demonstrated as follows:

Myocardium (either as perivascular infiltration or fibrosis)	14
Valvular endocardium (recent deposits)	5
Pericardium (recent exudate)	2
Arterial (aortic endarteritis)	4
Visceral (perivascular infiltration)	24
Spleen (enlarged)	3
Kidney (interstitial reaction)	24

Our attention was in the main attracted to the lesions of the kidney and reference will only briefly be made of the pathological processes in the other organs. The nature of the processes suggests a classification of the cases into acute, subacute (? recurrent) and chronic nephritis. Sharp lines of distinction do not exist between these groups, but typical examples of each are readily differentiated.

We are not unmindful of the finding of spontaneous lesions in the kidneys of rabbits by Ophuls. He examined 50 rabbits, some old ones, some used for physiological purposes, some previously injected with pneumococci, and others obtained from the market. Of these 50, 10 showed scattered areas of marked interstitial change, with the formation of depressions on the surface, and of these, 4 "proved to be radially arranged chronic septic foci." We have also observed depressions with productive interstitial change in the kidneys of old rabbits, but have missed them entirely in young rabbits (under eight months). For this reason less weight must be placed upon the presence of renal fibrosis in experimental animals which are old at the beginning of the experiment, or which, on account of the duration of the experiment over months of time, advance to an age over twelve or fourteen months. The presence of definite acute kidney lesions early in the experiment, and their absence in the controls of the same age is, to say the least, suggestive of their induced character. Moreover, the demonstration of the bacteria similar to those used in some of the lesions studied is also very significant. It is furthermore to be observed that the renal lesions of spontaneous character are scattered irregularly through the cortex and usually lie quite widely separated. The depressions are the size of small pinheads and are situated between the borders of two contiguous lobules. We have not observed spontaneous lesions causing a granular roughening of the surface of the individual lobules, though I can well see that such may occur if a susceptible animal be affected by a spontaneous infectious disease of long duration. The experimental lesions may be distinguished from the spontaneous lesions referred to by Ophuls by the more extensive dissemination.

Acute Stage of Experimental Interstitial Nephritis. Lesions in the acute stage were observed in the animals which died or were killed at short intervals after the inoculation. The tissue changes of this group were studied in animals receiving only a single inoculation, and which were permitted to live from two to thirty-three days. Toward the end of this period a considerable change in the picture was to be noted, though the reaction was of the nature of an acute process. The acute lesions were also studied in the cases in which repeated inoculations were made, but in only those in which the time from the first inoculation until death was under thirty-five days was the process a purely acute one.

Macroscopically little could be noted in the rabbit kidneys in the early stages which would give one a clew as to the character of the internal changes. Sometimes a swelling of the cortex and a gray or grayish-pink color of its substance suggested a "cloudy swelling." But the presence and distribution of the inflammatory process could not be recognized in the gross.

The first reaction following the inoculation was observed on the second day in the glomeruli. The capillary coils were intensely congested so that the entire glomerulus appeared enlarged and fitted snugly into its capsule. There was no intracapsular crescentic space. The cells of the glomeruli appeared swollen and some were vacuolated. A few lymphocytes were found in the glomeruli as well as about the afferent arterioles just at their point of entrance through the capsule. None of the glomeruli showed evidence of thrombosis or embolism and all evidence of severe glomerular degeneration was wanting. The convoluted tubules of the first order stained readily with oesin; the nuclear bodies stained poorly, and the cell protoplasm was granular. The majority of the cells were large and occupied the free space of the tubules. There was no evidence of fat or lipoid material in the cells by the microscope.

Where the time before death was increased, the degenerative changes in the kidney remained about the same, but the cellular reaction became greater. This reaction appeared to be distributed along the course of the vascular tree in the kidney substance. The arterioles of the intermediate zone (between cortex and medulla) showed the presence of an infiltration which was mainly lymphocytic, but which also contained plasma cells and occasional leukocytes. About some vessels the amount of infiltration was quite intense, but the character of the cells remained the same, and in no case was there evidence of destruction of the tissue of the involved area to form abscess. The infiltrating cells lay in the widened interstices of the stroma. The looseness of the stroma suggested an associated edema, but the striking feature was the perivascular distribution of the infiltrating cells. As previously indicated the arterioles of the intermediate zone were surrounded by wandering cells of the lymphocytic type, and from these a cellular reaction could be followed along the vascular branches into the cortex and to a lesser extent into the medulla. Elsewhere again an even more marked infiltration was found about the interlobular arteries, which extending from the medulla through the cortex led to the production of radiating bands of cellular reaction through the kidney substance. These bands of infiltration did not alone involve the cellular tissue about the interlobular arteries, but also spread into the surrounding intertubular stroma, so that the kidney tubules of the various orders lying in the interlobular region were surrounded by a cellular exudate. Fibrin was never noted in this exudate, and it was never observed to have purulent characters. Not only were the tubules surrounded by this infiltration but also the neighboring glomeruli. It is to be noted, however, that this inflammatory process in extending through the stroma remained isolated to the interstitial tissue and did not pass into the epithelium of the tubules. Only rarely were a few leukocytes found within the tubules. Likewise the infiltration remained for the most part on the outside of the glomerular capsules forming compact masses about them. The glomeruli themselves were the seat of cellular exudate only in proportion to the intensity of the individual attack made upon them. Some glomeruli were almost free from reaction, save a congestion and swelling of the cells as observed in the earlier stage. Others again showed the presence of many lymphocytes lying both between the capillary coils, as well as in the capsular space. In the early stages no proliferative response was noted in the connective tissues of any portion of the kidney.

Between these radiating bands of cellular infiltration the kidney substance was less involved in the process. Degeneration of the epithelial cells of the convoluted tubules was more advanced than was noted in the early stage. The epithelial cells were decidely granular and vacuolated but fat was not present. Some tubules showed erosion of the inner surface of the cells, so that an irregular and ragged lumen was produced. Frequently a granular debris was found within the tubules, but only exceptionally were wandering cells present. Where considerable degeneration with erosion of the epithelial cells had taken place the lumen of the tubules appeared enlarged, in sharp distinction to the compressed tubules in the zone of cellular infiltration and to the appearance of the tubules in the early stage of cloudy swelling. Here and there small islands of cellular infiltration were observed within the less involved portion of the cortex. These islands consisted of lymphocytes and plasma cells aggregated about the afferent arterioles of nearby glomeruli. In serial sections some of these periarterial reactions could be traced to the glomeruli. At times the related glomerulus was also infiltrated by lymphocytes, or showed a reaction of edema and congestion.

The changes noted in the glomeruli during this stage of the inflammatory reaction deserve special comment. Congestion and edema of the glomerulus and a varying amount of swelling of the epithelial cells lining the tufts appear to be the early reactions. I have never noted the obliteration of the circulation in the glomeruli during this stage, in fact, the capillaries appear to be unusually dilated and pressure effects could not be observed about the entrance of the arteriole. Subsequently both degenerative and progressive reactions may be found. Degeneration is mainly seen in the epithelial lining of the glomeruli and their capsules. The cells are no longer seen as slender spindles, but are more oval and bulky. Some are quite granular with poorly staining nuclei, while others have desquamated or have disintegrated, forming a granular debris. In a few instances I have been able to demonstrate small hyaline droplets in the epithelial cells of the glomeruli.

The cellular infiltration varied greatly in different portions of the cortex. This reaction was always lymphocytic and ranged from the presence of a few cells to considerable numbers lying scattered between the glomerular loops. In exactly what position these cells lay, whether free in the spaces between the loops or between the endothelial and epithelial cells could not be determined. Some cells, however, were found in the capsular space. These cells of an inflammatory exudate were not associated with an output of fibrin.

Lastly, in the later stages of the acute process a proliferative reaction was evident in the glomeruli. The capillary coils appeared very cellular. These cells were of spindle character and were disposed parallel to the direction of the capillaries over which they lay. Whether these cells were of an endothelial or epithelial character I am not prepared to say, but their presence was more marked in those glomeruli in which a lymphocytic reaction was less decided. These glomeruli showing proliferation were less congested and even appeared as if the circulation with them had been lost. This, however, was more apparent than real, for degenerative change, which could definitely be indicated as the result of proliferative occlusion of the circulation was not observed in any of them.

Undoubtedly, in the radiating bands of inflammatory reaction, the glomeruli as well as the tubules suffered pressure effects from the surrounding exudate. In many instances the tubules and glomeruli were small and compressed so that the usual spaces and lumina were obliterated, but even in the presence of this massive cellular reaction there was little tendency on the part of the wandering cells to pass through the glomerular capsule or the epithelial lining of the tubules.

True embolic lesions of the glomeruli were encountered in a few instances. In them a partial or complete obliteration of the capillaries of the glomeruli had occurred, and all were involved in a greater or less necrosis of the vascular loops. The glomeruli were represented by a homogeneous mass devoid of cellular elements, except for the presence of a few lymphocytes and occasional leukocytes which entered them from the surrounding tissues. At times these glomeruli were quite pink staining, at others there was a blue periphery. In some cases red blood cells were found in the spaces between the glomeruli and the capsules, but extensive and diffuse hemorrhages in the tissues and tubules were not noted. There was commonly a cellular infiltration about the glomerular capsule, which varied in the relative proportion of lymphocytes and leukocytes present, but in none was there evidence of abscess formation. In one instance the demonstration of Gram positive cocci mostly in pairs, but also in short chains of four and five, was readily made. These cocci were found in the glomerular coil, but their exact position in relation to the capillaries could not be determined. In two of the four instances showing glomerular infarction, the heart valves showed recent vegetations. The other two were free from demonstrable deposit, both in the heart and arteries. It would appear that the materials leading to the occlusion of the glomerular capillaries may develop in the circulatory blood, or that the lodgment of small embolic masses of bacteria within the glomerulus leads to a progressive thrombosis to which the greatest damage is responsible. In our microscopic preparations, although bacteria have been demonstrated in the necrotic glomeruli, we have not been able to determine the exact nature of the plug which occluded the blood current, for with the tissue dissolution of the involved glomeruli, fibrin, emboli, or thrombi might readily suffer such change as to destroy their structure.

The reactions occurring in the arteries, and particularly those of the kidney, are of great importance in analyzing the progressive changes in the kidney at different stages as well as in correlating the experimental findings with those in human renal disease. The arteries are important instruments through which noxious agents act upon the kidney substance, and in some cases (in the human) appear to be the prime factor in inducing, without other agents, sclerotic processes of the kidney, the primary contracted kidney (Jores). With this latter process, the induction of an arteriosclerotic renal sclerosis, our experiments have nothing in common. The renal arteries of all sizes show no evidence of proliferative or degenerative change which sufficiently alters the size of their lumina to interfere with the nutrition of the essential tissues. True it is in some vessels the endothelial coat appeared to be loosened from the underlying internal elastic lamina and a few cells were found in the new spaces. Some of these cells appeared like wandering cells, others had the characters of fibroblasts.

The arteries, however, appeared of great importance in acting as the means for distributing the essential element which induced the inflammatory reaction in various parts of the kidney substance. Not alone were the bacteria and it may be embolic particles, brought to the glomeruli, but, as we have shown by the remarkable distribution of the inflammatory exudate, the arteries were the important structures around which the reaction was found, and by which the inflammation was led through the cortex. The frequent proximity of the arteries to the veins makes it obvious that the perivascular reaction is also associated with the latter, as was pointed out by Ziegler. The interlobular arteries and the arteries of the intermediate zone always show the greatest perivascular response in all stages of the disease, and from these the afferent arterioles carry a similar, but lesser reaction to and into the glomeruli. The perivascular distribution of the inflammation was striking from the earliest beginning of lesions in our animals. We need not here repeat the details of the inflammatory process, save to remark that the cellular exudate was mainly lymphocytic, in which not a few plasma cells were found. Some leukocytes were present and, after several days, fibroblasts were evident in the neighboring connective tissues. The radiating character of the infiltration was alone due to the normal distribution of the arteries and the perivascular position of the exudate. The distance to which the inflammatory process extended into the neighboring stroma, surrounding tubules, and glomeruli varied in each case.

It is suggested that the perivascular distribution of the inflammatory products is dependent upon a richer lymphocytic supply of these tissues; either that the bacteria themselves find a more favorable environment or that their toxic products are collected or eliminated by this route. Upon the solution of this question we can give no evidence. It is, however, to be added that this perivascular position for the inflammatory product is not unique for the kidney structure alone. A similar reaction, though not so constant, was found in the meninges, diaphragm, voluntary muscles, liver, and joints, while with almost equal frequency to that of the kidney was it observed in the heart. The much discussed Aschoff's bodies of the heart, present so generally in acute rheumatic fever, are closely related, if not identical with the perivascular processes in the heart muscle observed in our cases.

A chronological classification of the renal lesions in our animals, as Loehlein made for the human cases of glomerulo-nephritis, was not possible, as the progress of the inflammation and the complementary reactions were by no means constant. Whereas a well marked perivascular inflammatory reaction was still present at the end of four and five weeks in some, others had lost all evidence of the exudate and had been restored to a normal looking structure. Here and there these healed lesions left areas of slight fibrosis, observed particularly in the vicinity of the interlobular arteries, or showed slight pericapsular thickening of the glomeruli. The connective-tissue increase in these tissues was so slight that we were willing to accept these cases as examples of healed nephritis. The amount of permanent damage in them was insufficient to interfere with the function of the kidney.

SUBACUTE STAGE OF EXPERIMENTAL INTERSTITIAL NEPHRITIS. The lesions in the subacute stage are distinguished by the less intense cellular infiltration with evidence of fibroblasts in the involved stroma, as well as by the greater and more diffuse degenerative changes in the epithelium. The character of the cellular elements found in the exudate was similar to those in the acute stage, though the leukocytes were almost wanting and plasma cells were present in greater numbers. The position of the exudate remained perivascular. Commonly focal areas of a more acute character were found in the same kidney in which the subacute processes were the outstanding features. With all the changes in the perivascular tissues, the arteries showed no sclerotic process in the media or intima which could interfere with the circulation. Fibroblasts and newly developed connective-tissue cells were present in fair numbers in the adventitial stroma, as well as in the supporting framework of the tubules bordering the arteries. Thus the radiating and band-like involvement of the cortex was maintained, and frequently the insertion of these bands into the capsule of the kidney was well marked. Slight depressions on the surface of the organ marked the points where the cortex was involved in proliferative and degenerative change.

The tubular lesions were of two kinds, those in the areas of interstitial involvement and those in the intervening portions where the stroma showed no change. In the former, atrophy and compression of the tubules in the path of the connective-tissue change was well marked. The convoluted tubules of both the first and second order were much shrunken and the lumina narrowed. Fatty changes, in the form of fine granules, were found in the epithelial cells of only a few of these tubules. On the other hand, the tubules in the intervening portions, where the stroma was not involved, showed enlarged lumina, with eroded epithelium and frequently a granular debris on the surface. Fatty changes were not encountered in these structures.

A variety of changes were also present in the glomeruli. Those of a proliferative character were mainly evidenced in a cellular increase of the glomerular loops with occasional connective-tissue thickening of the outer layer of the capsule. Proliferation of the glomerular epithelium, both upon the coils as well as the inner layer of the capsule was not uncommon. A granular debris with exfoliated cells occupied the crescentic space within the glomerular capsule while occasional lymphocytes were still present in the structure.

On the other hand, a degenerative process, the presence of a hyaline band or deposit was quite often observed bordering the capillary loops of the glomeruli. In some glomeruli almost all of the capillaries showed the presence of this deposit while in others it was limited to individual loops. The deposit was of a hyaline type which appeared immediately outside the endothelial coat of the capillaries. No evidence of a glomerular epithelium could be distinguished upon the coils of the capillaries involved in the degenerative process. The development of this hyaline deposit simulates very closely the process of hyalinization of the glomeruli in the human kidney, as has been described by a number of authors (Vollhart and Fahr). It appeared particularly in the subacute form of a glomerulonephritis or during the stages of repair following an acute lesion.

All degrees of destruction of the glomeruli were evident. Some showed a hyaline process in but a few capillary loops, others had a greater involvement. The presence of blood within the glomeruli varied with the extent of the changes in each coil. Where the hyaline deposit was more advanced, the presence of connective-tissue lamellæ, following the tortuous course of the capillaries, or lying concentrically arranged on the inner surface of the glomerular capsule was always noted. Where the capsule itself showed a fibrous thickening, there were synechiæ which bound the glomerulus to it. These adhesions were most marked at the base of the capsule where the bloodvessels entered it, and from here it advanced until the glomerulus was completely bound. In no instance was a fibrinous exudate found by which a granulation tissue could lead to fibrosis in the stage of repair. It would appear rather that the connective tissue was stimulated to growth mainly through the injury induced upon the glomerular tissues (with its exfoliation of the epithelial lining of the capillaries and capsule) as well as the direct effect of the bacterial irritant upon the interstitial stroma. The complete obliteration of some glomeruli by a hyaline fibrosis was not uncommon. In these, there was no evidence of any patent capillary loops.

Chronic Stage of Experimental Interstitial Nephritis. The chronic stage of the disease was characterized by the development of fibrous tissue in the radiating perivascular bands previously noted, the sclerosing of the involved glomeruli, the atrophy and compression of many tubules of the cortex, and the almost complete absence of wandering cells. Macroscopically the surface of the kidney was puckered and coarsely granular, the depressions being more frequent than the isolated pittings arranged at the points of intersection of the borders of the lobules. The best results were observed in those animals receiving several inoculations of the same organism at intervals over a fairly long period. Well marked examples were obtained in animals 31 and 33, living 148 and 163 days under observation respectively, while lesser degrees of the chronic stage were noted in animals 28, 29, 30, and 34, surviving from 113 to 228 days after the treatment was started.

It must be remembered that in keeping young animals under treatment for from three to seven months, adds a sufficient time period to their lives to put them in a class in which a certain number of them spontaneously develop some fibrosis in the intermediate zone and along the main interlobular arteries. The more widespread character of the fibrosis, in our experiemnts, following not only the interlobular arteries, but also their branches and advancing to and into the glomeruli, gives, we believe, some distinction for the differentiation of the lesions. Moreover, it was found that when the animals had recently received an inoculation, evidence of a recurrent acute non-suppurative infiltration was at hand in those areas previously discussed.

Where the fibrosis is well developed the tubules are shrunken and small. Some tubules contain hyaline plugs while others show only a slight amount of granular fat. The involved glomeruli are obliterated by a hyaline fibrosis. In the portions of cortex between the masses of connective tissue the tubules appear fairly normal, some are large with dilated lumina. The uninvolved glomeruli are larger than normal, and at times appeared quite cellular. The retraction of the cortex opposite the areas of fibrosis was unusually well shown, and appeared to result as an active process from degeneration and loss of parenchymatous tissue of the part as well as a shrinkage of the connective tissues, rather than from the bulging of the intervening kidney substance in a process of compensatory regeneration. Little evidence of cellular regeneration of the parenchymatous tissues was at hand, save for the enlarged convoluted tubules and some proliferation of the epithelial lining of the enlarged glomeruli.

In general the results of these experiments indicate that a true nephritis may be experimentally induced in rabbits by the inoculation of culture of the different types of organisms belonging to the streptococcus viridans group of bacteria, isolated from man. The response to this infection was the production of a non-suppurative inflammation, lymphocytes and plasma cells being the chief constituent, which was distributed along the renal vessels and their branches. Varying with the intensity of the tissue reaction a variable amount of parenchymatous structure was involved which later suffered from the contraction of the healing stroma, as well as from nutritional change in consequence of glomerular obliteration, as has been pointed out by Loehlein and others. The primary toxic effect of the infection directly upon the parenchymatous tissues was transient and disappeared after the infection had been overcome. The isolation of the inflammatory reaction along portions of the renal arterial system gave an unequal distribution through the kidneys, which subsequently caused an irregular pitting and coarse granulation of its surface. Suppurative processes were never found.

The glomeruli were the seat of both proliferative and degenerative reactions. The former appeared to result from the direct effect of toxic substances arising in the process of infection and was accompanied by a slight lymphocytic infiltration, while the latter was associated with nutritional changes. The production of hyaline fibroid glomeruli was the usual outcome of the involvement of these structures. The embolic occlusion of a part or the whole of the glomeruli was noted in a number of instances, and although not necessarily associated with vegetations upon the heart valves simulated that reported by Gaskell and Baehr in man.

We would draw particular attention to the simultaneous occurrence of glomerular and perivascular lesions in these animals, as a response to a common agent, the streptococcus viridans group of organisms. Much has been discussed in recent literature of the importance of the streptococcus infection in heart disease, scarlet fever, measles, acute rheumatic fever, in inducing a distinct type of Bright's disease distinguishable from others. In these studies attention has been concentrated upon the glomerular lesions, viewing these as the primary and direct cause of the subsequent sequelæ. Thoma, Ziegler, and Vollhart and Fahr take it that the degeneration of the tubules of the cortex develops in consequence of the nutritional change induced through the obliteration of the glomerular capillaries. The fibrosis about these tubules is viewed as a type of replacement fibrosis which arises passively with the atrophy and disappearance of the parenchyma. Through our experiments, as well as by the examination of human materials, we are led to believe that a perivascular inflammatory reaction is present in the early stages of the glomerular nephritis induced by the streptococcus viridans group, and that a simultaneous proliferative reaction is present in the glomeruli as well as in the stroma of some of the renal arterioles. Furthermore, from our findings, the lesions of the inner coats of the arteries play no important part in the progress of the early or late stages of true interstitial nephritis which, in the end, leads to a type of renal sclerosis. The presence of embolic masses in the glomeruli is only an accident befalling the lesser number of these structures, and causing new complications in an already diseased tissue. Glomeruli in which no embolic process has occurred may suffer a sequence of changes which, in the end, through obliterative hyaline fibrosis, cannot be distinguished from those so affected. The peculiar hyaline degeneration which develops in the subacute stage as a band-like deposit along the borders of the capillary loops of the glomeruli (shown best by the phosphotungstic acid hematoxylin) deserves still greater attention than has been given it, and its elucidation may greatly assist in the explanation of the variable occlusion of greater or less numbers of the capillaries of the glomeruli.

Although the involvement of the glomeruli plays a most important part in the incapacity which the renal parenchyma suffers in this type of kidney disease, the perivascular inflammatory process with the progressive secondary involvement of tubules plays no small part in the final structural change of the organ. The contraction of the kidney substance appears to be a progressive process, resulting from a true inflammatory reaction in the stroma.

Associated inflammatory processes of perivascular arrangement found in the heart, liver, joint capsules, and other tissues suggest a common mode of attack by these streptococci upon many tissues. These findings broadly support the observations of Gull and Sutton, who, studying the late lesions of nephritis, commented upon the perivascular fibrosis, which was found not only in the kidney but in other organs and tissues of the body.

Moreover, the acute stages of non-suppurative nephritis in man, as have been admirably described and commented upon by Councilman (1897), are capable of reproduction in animals. The importance of glomerulonephritis in scarlet fever, penumonia, and infective endocarditis was at that time pointed out by him. Le Count has recently reported results similar to our own, in which the streptococcus pyogenes of low virulence was used in animal experiments.

The degenerative processes which accompany the inflammatory lesions of the interstitial tissue and the glomeruli consist in the main of a finely granular albuminous precipitate in the protoplasm with the occasional development of a peculiar coarsely granular or globular proteid deposit in the cytoplasm of the convoluted tubules. Fatty degeneration appears to play no important part in the degenerative process. In part at least this parenchymatous degeneration results directly from the effect of the bacterial toxins, as it is observed in the convoluted tubules associated, as well as not associated with glomeruli that have shown circulatory obstruction.

The proliferative changes which occurred in these experimental lesions, leading eventually to a chronic interstitial nephritis or renal sclerosis, have no relation to the fibroses of the kidney which develop secondary to arterial lesions. Jores has fully discussed such processes in man, indicating that an arteriosclerotic process which may effect the renal arterioles as well as those of other organs, and in which the aorta and large arteries may be but slightly involved, leads to a nutritional atrophy of the kidney parenchyma followed by a localized or diffuse fibrosis. Primary arterial lesions were wanting in the kidney of our experimental animals, while the early stages of the renal disease were characterized by the presence of true inflammation. We can, however, well appreciate that in experiments over more protracted periods, and in kidney affections of man, where similar circumstances initiate the process of disease, subsequent arterial affection may induce a vicious circle and lead to changes referable to an obstructed circulation as described by Jores.

What is important to appreciate, is that a form of acute interstitial nephritis induced in animals subsequently gives rise to a renal sclerosis of the type known as chronic interstitial nephritis. We believe, moreover, that a similar process is common in man and that the vascular sclerosis plays a secondary role in bringing about the contracted kidney.

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Reprinted from the Proceedings of the Society for Experimental Biology and Medicine,
1915, xii, pp. 199–201.

121 (1053)

Inhibition of sodium oleate hemolysis and toxicity by cholesterin.

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The hemolytic quality of soap solutions and particularly of sodium oleate has been studied by a number of investigators (Sachs, Meyer, Moore). Meyerstein later showed that the oleate hemolysis could be inhibited by lipoids, cholesterin, serum and organ extracts. Sodium stearate and palmitate are less active than the oleate. Moore has shown that the laking qualities of the soaps are in proportion to the unsaturated bonds of the fatty acids and that by iodine saturation can be inhibited.

The toxicity of soaps was studied by Munk who found that the quantity equal to 0.11 to 0.13 gram oleic acid per kilo body weight killed rabbits. In his experiments he introduced these quantities very slowly. The heart action was depressed, but continued longer than the respiratory function.

We have given rabbits sodium oleate intravenously. A 5 per cent. solution of anhydrous sodium oleate (Merck) in normal saline was used. The soap solution was injected into the ear veins in a single and rapidly given dose. Doses of 0.1 sodium oleate per kilo appeared very irritating, the muscles of the extremities were thrown into spastic contractions and the animal had convulsive seizures. The ill effects lasted for a minute and a half when the animal would show great depression with rapid breathing. The muscles then became quite limp; within an hour the animal was fully recovered. Doses of 0.13 gram per kilo weight were fatal. These animals would sometimes enter a convulsive seizure before the injection was completely made. The blood of these animals after death was not perceptibly laked and it would appear that in the animal body the quality of laking and that of toxicity were separate. When, however, the solution of sodium oleate was mixed with an equal quantity of cholesterin the toxic qualities were inhibited. This cholesterin sodium oleate mixture was prepared by adding 5 per cent. cholesterin to a previously prepared 5 per cent. solution of sodium oleate in normal saline, and heating in a water bath for several hours. A milky and permanent emulsion was thus obtained which was found to contain no free cholesterin but was filled with great numbers of anisotropic bodies. These bodies are probably cholesterin-sodium-oleate compounds and are not the pure cholesterin esters described by others. This emulsion may be inoculated intravenously in doses containing double the quantity of the lethal sodium oleate. Irritating effects were still observed in spastic muscular contractions but there were transient. The emulsion inoculated intraperitoneally produced some inflammatory reaction with slight fibrin exudate. A single intravenous dose led to no permanent injury in the animal, but repeated inoculations every second day, led to much wasting, so that one animal in a period of twelve days lost 900 grams. Such animals when set at rest rapidly recovered. It is possible that the toxicity of the soap solution may be still further masked by increasing the cholesterin to saturation. In this state, however, the compound is very gelatinous and hard to handle, while the addition of water for further dilution again leads to dissociation products.

Animals treated with the cholesterin sodium oleate mixture show no evidence of excretion of these substances in the urine. The compound readily circulates in the blood and is not filtered out by the capillaries. The lungs are quite free from change. We have noted, however, that frozen sections of formalin-fixed tissue showed anisotropic globules and an unusual amount of (?) cholesterin spicules in the liver parenchyma. The liver appeared quite yellow and fatty but the fat did not exist as the coarse globular fat of fatty infiltration. In these experiments we did not find the enlarged fatty adrenals as were present in another series in which the cholesterin materials were fed to the animals. The fate of the cholesterin and soaps has up to the present time not been determined.

The same cholesterin sodium oleate emulsion was used to demonstrate the inhibitory qualities of cholesterin upon soap hemolysis. It was found that 0.05 c.c. of a 5 per cent. solution of sodium oleate would hemolyze 1 c.c. of a 1 per cent. suspension of human blood cells in less than 18 hours at room temperature. On the other hand, 1.2 c.c. of the cholesterin sodium oleate compound did not hemolyze a similar quantity of blood. It was likewise found that the addition of normal serum to any mixture of sodium oleate and cholesterin still further inhibited the hemolysis and toxicity of the soap.

It is quite easy to prepare solutions of soap containing different quantities of cholesterin and by this means, observe the inhibitory influences of this substance. We have found that the 5 per cent. solution of sodium oleate in saline with the addition of 5 per cent. pure cholesterin is the most useful for study and is easily handled. The histological changes in tissues resulting from abnormal quantities of fluid cholesterin compounds will be reported upon later. By this combination of soap and cholesterin we have a means of introducing this otherwise inert substance in a fluid state which is assimilable.

Reprinted from the Proceedings of the Society for Experimental Biology and Medicine, 1915, xii, pp. 159–161.

94 (1026)

Experimental calcification.

By **Oskar Klotz** and **May E. Bothwell.**

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In 1905[1]–6[2] one of us was interested in the process of pathological calcification and indicated that in the human the condition was directly related to an antecedent fatty change in the tissues. From the studies then made it was demonstrated that the main factor leading to calcification of diseased organs was the accumulation of fatty materials in necrotic areas. The fat in these areas was liberated by the death of cells or was attracted to the areas of necrosis by the products of disintegration. The latter has been further demonstrated in the accumulation of fat by hyaline and amyloid substances.

Further proof of the relationship of fatty materials to the process of calcification is offered in a series of experiments where fats have been inoculated intravenously into rabbits. Two rabbits have been inoculated with pure olive oil and three with a mixture of cholesterin and olive oil (1–15) by the ear vein. Doses of 0.5 to 1 c.c. were given over a period of from one to eight weeks. The animals withstood the inoculations very well and showed no loss in weight. Temporary respiratory difficulty was sometimes observed for the first hour. The cholesterin mixture was usually warmed before giving.

The best results were obtained with the cholesterin-olive oil mixture after a period of four weeks. The major quantity of the oily injection was filtered out by the lung capillaries and only relatively small amounts reached the distant organs in its original condition. Reactions were recognized in the lung tissue at the end of two weeks when active proliferation of the endothelial lining of the capillaries frequently occluded their lumina or distorted the channels of the arterioles. The proliferating endothelium phagocyted the oil globules and frequently split the larger masses into small fragments which then were scattered through the protoplasm of these cells. The intracellular position of the fat could be observed during all stages of the experiment. In other instances, the phagocyted fat was removed from the blood channels and passed to the lymphatics. Such fat then appeared to lie free and not within cells. In the arterioles the fat appeared both in the proliferating endothelial cells as well as in deeper portions of the intima and media. In the latter structure it was commonly observed as an extracellular deposit. It was not uncommonly seen that the endothelial cells contained both fatty masses and cholesterin crystals. These crystals lay in clefts quite apart from the oil globules.

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[1] *Journal Exper. Med.*, 1905, VII, p. 633.

[2] *Journal Exper. Med.*, 1906, VIII, p. 322.

By staining with sudan all the oil masses were equally colored. Sections stained with Nile blue sulphate showed the presence of neutral fats, fatty acids, and intermediate mixtures of these. With the polarizing microscope some anisotropic globules could be seen, while free cholesterin plates were also demonstrated. The majority of the fatty acid globules were intracellular. These were usually smaller than the globules of neutral fat. The fatty acid racidal was also demonstrated by the Fischler method.

Associated with the intra- and extra-cellular fatty acid globules, was found the deposition of calcium salts. The calcium became precipitated in the borders of these fatty acids and gradually irregular calcium precipitates encroached upon the center of the acid globule. This deposit took place in the protoplasm of the large phagocytic cells as well as in the fatty deposits which were lying free in the tissue or in the lymph channels. At the end of eight weeks we found the lung substance filled with these minute calcareous masses lying in areas of cell proliferation looking not unlike small tubercles. The calcareous process was also recognized in the walls of the blood vessels. In the latter, the process occurred in the deep intima and media where fatty deposits were also demonstrated. These calcium salts were recognized by staining with hematoxylin and their phosphatic radicals with silver nitrate. They could be removed by treating the tissue with hydrochloric acid.

By the method here employed one is able to demonstrate the intimate association between the abnormal presence of fats and the process of calcification. It is furthermore shown that the endothelial cells of the capillaries of the lungs have the property of splitting fats and liberating the fatty acid radical. By microchemical means the stages in the process may readily be followed.

As the fat within the endothelial cells has been phagocyted and lies in vacuoles in the protoplasm where it is acted upon by lipolytic secretions of the cell, it differs but little, in relation to cell activity, from fatty deposits which are extracellular and are acted upon by lipases present in the serum. In other words, the phagocyted fat of endothelial cells has an entirely different bearing to the cell from the accumulation of fats in fatty degeneration.

Our present findings are in perfect accord with the views we have formerly expressed upon the process of pathological calcification.

Reprint from The International Association of Medical Museums,
Bulletin No. V. June 1, 1915

A MODIFIED JORES' METHOD FOR THE PRESERVATION OF COLORS IN GROSS SPECIMENS.*

By Oskar Klotz and W. W. G. Maclachlan.

(From the Pathological Laboratories, University of Pittsburgh)
Pittsburgh, Pa.

The Jores' method for the preparation of museum specimens aims at the preservation of the colors in anatomical and pathological tissues. In general the aim is similar to that of the Kaiserling method, but it possesses certain qualities which make it preferable to it. The Jores' method is easier of application, cheaper in preparation and brings out color reactions seldom obtained by other methods. In our hands, it has been much simpler to apply to all types of tissues and does not need the close attention for changing the specimens to the succeeding solution. Moreover, the specimens never diminish in the brilliancy of the colors during any stage of the process, and we have not been troubled in having to deal with specimens which have been overdone in the first solution, as is frequently encountered with the Kaiserling method.

In the Kaiserling method, there are three stages in the preparation which must be appreciated,—fixation of the tissues, restoration of the color, and preservation. In the Jores' method, there are only two stages, since the color is never lost from the first, and requires no restoration. The alcohol treatment of the specimens (Kaiserling No. II) falls away entirely. Moreover, with the small percentage of formalin in the fixing solution, the specimens remain pliable and do not tend to shrink irregularly. In order to obtain the best results all specimens must be thoroughly washed in normal saline solution before being placed in the Jores'. This procedure is merely to clean the surface of the tissue, and do away with adherent debris.

The fixing solution recommended by Jores was as follows:

Karlsbad salts	5
Chloral hydrate	5
Formalin	5
Water	100

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*Read at the meeting of the International Association of Medical Museums, Toronto, April 9th, 1914.

In following this prescription we have met with some failures which were in part accounted for by the commercial Karlsbad salts used. We have, therefore, made up a modified Karlsbad salt of the following composition:

Soda Sulphate	22
Soda bicarbonate	20
Soda chloride	18
Pot. nitrate	38
Pot. sulphate	2

Furthermore, we have found that in using a considerably weaker solution, and increasing the time of fixation from 2 to 10 days, the results were more striking. At present, we use the following combination, which improves considerably after standing for a few days.

Modified Karlsbad salts	125
Chloral hydrate	125
Formalin	125
Water	4000

On account of the weaker formalin solution, the penetration of large organs is more rapid, and we do not have the leathery covering produced, which was so commonly found in the Kaiserling preparations.

The colors in the depths of organs are preserved equally well as on the surface. This is often of advantage in trimming specimens after fixation.

When thoroughly fixed the specimens are washed in cold running water for 6 to 10 hours. This is important, as it is advantageous to remove all the salts and formalin before placing the specimen into the preserving fluid. Jores advises the use of the Kaiserling III fluid for final preservation. We have, however, preferred Frost's fluid, leaving out, however, the sodium fluoride from the solution.

Cane sugar	3500
Pot acetate	160
Chloral hydrate	80
Thymol water	8000

Reprint from The International Association of Medical Museums,
Bulletin No. V. June 1, 1915

THE STAINING OF PATHOLOGICAL SPECIMENS IN THE GROSS.*

By Oskar Klotz,

From the Pathological Laboratories, University of Pittsburgh, Pittsburgh, Pa.

At the meeting of the German Pathological Association in 1913, Benda reported upon the staining of gross specimens with sudan. Concurrently with his experiments we were carrying out similar methods, applying them to a greater variety of tissues than reported on by him, and applying other combinations of stains to demonstrate more clearly the characters of tissues in gross specimens.

The staining of tissues containing fats and lipoids by sudan, scharlach-roth, or alkanin has found excellent application for student demonstration. This is particularly true where small quantities of fat are frequently not properly appreciated by the student unfamiliar with the disease process and the varying picture so frequently induced in different stages of the same process. Moreover, preparations preserved by the ordinary methods of museums (Kaiserling or formalin) do not bring out the presence of fatty deposits but on the contrary, with age lose the natural differentiation of fat from the surrounding tissue. Benda as well as Jores found a favorable application of the sudan method in the staining of the arteries by sudan. This, as is shown in our demonstration gives excellent results and shows the presence of fat in minute quantities in lesions both superficial and deep. The intimal streaks of the aorta appear with unusual brilliance. Atheromatous plaques with the overlying endarteritis differ in the intensity of the color according to the mass of endarterial thickening. The results are not so striking in the advanced atheroma with ulceration, as in them, the fatty change is diffuse over all surfaces of the vessel as well as in the isolated atheromatous plaques.

The differentiation of fatty infiltration and fatty degeneration of the heart is also well shown, and I know of no better method of preserving demonstration specimens of these lesions.

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*Read at the meeting of the International Association of Medical Museums, April 9th, 1914.

Another striking application of the sudan staining is obtained in cancer of the breast, where the surrounding fat tissue takes the deep orange stain while the cancerous area remains unstained or a pale pink. Not uncommonly such specimens demonstrate the development of metastases in the surrounding stroma which, in the unstained specimen, are difficult to recognize. The cancerous masses stand out in such contrast that, for the teaching of gross pathological specimens, it is of great aid.

Again, in fatty changes of the liver, be these diffuse or lobulated, the sudan staining brings out the changes in the tissues very clearly. Fatty changes associated with portal cirrhosis may be counterstained with haematoxylin subsequent to the sudan treatment. Tuberculous processes are also well demonstrated by this method.

The method consists in fixing the tissues in formalin until thoroughly hardened. They are then trimmed ready for mounting and rapidly washed in 60 per cent alcohol. The specimens are then placed in a saturated solution of sudan in 70 per cent alcohol and allowed to remain for three days to a week in this solution. When removed they are washed in water for several hours and then allowed to remain in a jar of 5 per cent formalin until the excess adherent sudan is removed. The specimens are permanently mounted in a 5 per cent formalin solution. The specimens counterstained with haematoxylin are treated for about 20 minutes in Boehmer's alum haematoxylin subsequent to the sudan treatment. These specimens are then blued to the desired color in an alkaline water.

Another useful and rapid staining method for gross specimens is obtained by the use of a two per cent aqueous solution of acid fuchsin. By this means the connective tissue stroma can be readily demonstrated, and even the fine trabeculae illustrated in a manner not obtained by the ordinary methods of preservation. The specimens remain in contact with the stain for 15 to 60 minutes, are rapidly washed in water and then allowed to remain in 95 per cent alcohol for several hours. Such specimens are not permanent, and are used soon after preparation for class demonstration. If placed in absolute alcohol, the color can be preserved for weeks. This method has found useful application for demonstrating fibrosis of breast, lung and liver.

ADDRESS TO GRADUATING NURSES,

MERCY HOSPITAL,

OCTOBER 13, 1915.

Members of the Graduating Class:

You have long looked forward to this hour, when each of you would be passing an important milestone in your life. Each of you has, I hope, had an ideal before you, which, when you entered upon your studies and training for nurses, was clothed in the highest principles. Your model may have been gained from the work of many worthy sisters, from your innate motherly desire to render aid to fellow beings or from the determined success of Florence Nightingale,- a worldly woman with heavenly ambitions. Undoubtedly, many have entered upon their profession, little realizing that the ideal could not be gained without many personal sacrifices. You were brought to appreciate how soon our thoughts are bent to view the common-place misfortunes, the ills of our fellows, their sorrows and troubles, to forget ourselves, while our daily routine absorbs our interest until the loose strings of our ideal tend to slip from our hands. It is now for those of you with steadfast purpose to cling to those early convictions, placing

your profession on the high pinnacle of desire, and strive to make yourself one of whom others shall be proud.

An unselfish life must be yours. Your years of study and preparation must have shown the limitless field that lies before you. Not all your training can be obtained from books, or class or ward demonstration. These can only direct your hands to ease the pain of illness or accident. It is only your inner sympathy and truth which can win the confidence of your patient, relieving her of much mental distress, and anguish far harder to bear than the hurt of wounds.

As you are now passing the flood-gate of pen-up enthusiasm, to be freed over a boundless sea of endeavor, you are temporarily blinded from viewing in proper perspective, your future work. The way is open to follow many trails. Which shall it be? You are beset by the old proverb that "so long as more remains to be done nothing seems done." To you your deficiences seem glaring, and you are conscious that you are still far from your early ideal.

If such be your reasoning, I predict you the fullest success. Your ideal must ever be before you, leading you onwards and indicating the never-ending demands upon your sacrifice.

There is a time in the life of everyone, when each must take his allotted place in the community. Our presence is recorded in common statistics to swell the number by one. The count is the same for each, and as we stand shoulder to shoulder with our fellow men the yard-stick shows us no greater, no less, than the next. The great armies in the field today are recorded by our daily papers as so many thousand men strong. In looking down the vast lines of rank and file, little difference distinguishes the face or the physique. The distinction by name has fallen away as walueless, and family record- a long line of ancestors bold in adventure or strong in enterprice- has given place to a cold official number. The death of private 78, 162 has caused a gap in the ranks which must be filled. Immediately the mechanism of orderly organization fills the gap, and the loss of 78, 162 is forgotten.

So, too, you and I are standing in a rank and file, one among many. We have a duty to perform, and must ever be ready to fill the gap of opportunity,- not, however, as in war to await a comrade's misfortune, but to stand at sentinal duty and alert at our post. Are you prepared? ! Our presence, this afternoon at this

gathering is the answer. Your manifold training has been in preparation for your answer, tomorrow your call to duty is the obligation you bear to the community, to take your place shoulder to shoulder with your fellows and answer the roll call to number 78, 162.

During your years of training you have come in contact with much that was new to you, and have seen the application of the science and art of healing. There was a time when medicine was chiefly an art with little science applied. Those were the days of secrecy, when little was it desired to have anyone have a knowledge of the potions administered to the patient. Each physician rivalled his colleague in his suave approach to the patient, his knowledge of natural remedies and his ability in prescribing polychromatic polypharmaceutical pills. The longer the list of ingredients in his medicine, the greater potency was assigned to it. The nurse at his command was but an attendant, to carry out a fixed routine, like a piece of machinery, but without personal knowledge or interest in the patient. Time has changed all this. Assistance to the sick is guided by reason;

gradually one by one of the alleged remedies have been struck from the lists in the materia medica, until our faith has been severely shaken from all but a few drugs. Instead of copious volumes dealing with the useful properties of every weed that grows, our pharmacopaea has shrunken to an emaciated volume with anaemic contents. No more does the author extole the properties of this or that drug, but only suggests that such an one may be tried, he having found it useful in a similar case. More frequently, the successful management of disease rests in a proper knowledge of its nature and course, permitting the giving of judicious advice and tender care. The latter particularlry rests in your hands.

It is interesting to throw a casual glance over modern medicine as we know it today, and to view the trend along which its newer paths are directed. Granting, of course, that a keen interest has been long present in the old workers of the field of medicine, there was a definite time when a revival and new impetus was given

to its study. Up to the beginning of the 19th century or better perhaps until about the middle of that century, the various accessory facilities for learning more about disease and its prevention, had been used up, so that many of the problems of disease appeared impossible of solution. In rapid succession, however, new discoveries were made, some of which, though not in the immediate field of medicine, had a very important bearing on its future. In 1846 Morton demonstrated the use of ether as an anesthetic, making possible remarkable surgical procedures which previously were unavailable because of the infinite suffering entailed during the operation. How the field of surgery has grown since this date can hardly be expressed although those who are in contact with the work at the hospitals realize the greatness of the discovery of anesthesia.

Shortly following this, through the interest of a chemist, attention was attracted to the part played by bacteria in changing the chemical nature of fluids. Pasteur demonstrated the bacterial nature of fermentation

and by a comparison with tissues undergoing decomposition suggested the disease producing function of other micro-organisms. We can well appreciate how the brilliant minds of his time hesitated to give any weight to this suggestion and some even were abusive in denouncing his revolutinary forebodings. Bacteria, although known to be existing, were regarded more in the light of curiosities than important living forms to be taken seriously. The almost dramatic demonstration of bacteria in the animal body in disease and their absence in the normal individual soon gave weight to Pasteur's belief and stimulated many followers in his new discovery. Difficult though it was to bring forward the final evidence that the presence of bacteria indicated the causative agent of disease, sufficient proof has been given in not a few, to bring a new understanding to many forms of illness. However, a mere understanding of the nature of disease and its cause is insufficient for the patient and profession. It is true, causative agents must be determined, but when once established, the next step is to find a means of combating them. And here we have the development of an entirely new line of work which previously had no

rational basis for study. When, however, bacteria were shown to be the agents of definite disease and these bacteria were studied from every view point so that they became known to the investigator in all their peculiarities, then and only then, could the subject of cure be approached with any hope of success. Much of this success has been already attained, but as you know, there is yet much to be done.

It was directly through the investigations of Pasteur that Lister was able to offer his new discovery to surgery. His was, that with the knowledge of bacteria we can make surgery a safe proceeding, robbed of the unfortunate suffering seen in the older work. Many a successful operation had lost its patient because of subsequent bacterial attack. This danger now i~~s~~n aseptic and antiseptic surgery has been reduced to a minimum.

These three important findings of anesthesia, the bacterial nature of disease and aseptic surgery falling between the years 1847-1867 have had a most important bearing in the advances that we appreciate in medicine today.

More interesting to us here gathered is the close association

of the progress of the nursing profession and all that goes with it, in these advances in medicine. Beginning with the organized work of Florence Nightingale in 1854 there has been a continuous advance in the methods and scope of the nursing profession until at the present day the many new fields that are offered to properly trained graduates, is all but limitless. Not a few of the members of the nursing profession have played a direct part in the furtherance of medical investigation. This more recently has been in the direction of the social service work. Problems of hygiene and preventive medicine are directly allied to this field and in it we seek the important advances of the nemt decade. Nowhere can we apply the doctrine of "an ounce of prevention is worth a pound of cure" better than in human illness, and though our resources were first in the hands of hygienists alone, the broader dissemination of this knowledge in the medical and nursing profession and even the laity will do much to control preventable disease. The nurse by careful instruction of the patient and the family,is in the position of a community agent, the value of whose work is more

evident by acts of omission than receives credit when properly performed.

What can be accomplished by a single individual, whose heart is in her work, could be illustrated in many lives. One with heroic qualities comes to mind. Jeanne Mance, the descendant of an honorable and influential family in France, sailed for America in 1641. She had joined a party of adventurers to settle in America and help the newly established colonies in their struggles with the Iroquois. Through the benevolence of a Madam Bullion, she was given charge of an endowment of 42,000 livres. Reaching Quebec on the St. Lawrence, Jeanne Mance soon continued her journey up the river, to the new settlement of Ville Marie where she with a few followers located one of the earliest hospitals in America. The hardships entailed in the erection of the small log building, the fear of the marauding Indian, the difficulties of procuring food and hospital supplies gave constant worry to the handful of settlers. Through it all, the splendid spirit of Jeanne Mance gave courage. Her little hospital, was always taxed to its capacity, and though once burned was re-

erected and built on a larger scale. Epidemics of scurvy and small pox then appeared in the growing community- and still Jeanne Mance came to the front. As directoress of this isolated institution, she took charge of all sick, Christian and heathen alike. Hers was an unselfish life, the benefits of whose sacrifice has been reaped by suceeding generations. Her spirit still pervades the haunts of her former mission, for today her work is being carried forward by the Sisters of Hotel Dieu in Montreal. Almost upon the spot of the original small hospital of twelve beds, stands the Hotel Dieu, through whose portals have entered thousands of afflicted to receive the blessing established by Jeanne Mance.

It may not be your immediate desire to have your name chronicled upon the pages of history, but none the less, your good work shall be recorded to swell the annals of success of your fellow alumnae of Mercy Hospital. You shall carry forward the torch. Keep its flame high to brighten the paths of those placed in your charge. Your mentors shall follow you with a keen interest, shall partake of the pleasure of your success, and shall ever stand ready to help and advise you in your difficulties. The

home of comfort may be awaiting some, more often, however, your steps shall be among those deprived of worldly luxuries, who, nevertheless, in their humble way, are rich in the gift of appreciation. This you will come to value beyond all mometary return, and oft you will turn your head in the direction of such grateful patients, who by actions or words, make you feel, that you, too, have done your little part in easing pain. Your profession is a noble one and the world awaits you.

The Mercy Hospital extends to you its best wishes, and to each and all, the best success.

Oskar Klotz.

THE CANCER PROBLEM,

by

Oskar Klotz

(Read at the Meeting of the Allegheny County Medical Society, June 28,1915).

The cancer problem or better the problem concerning the origin and development of malignant new growth has made considerable progress in giving us a better understanding of the varied factors concerned, but nevertheless, still it leaves us much in the dark of the actual principles underlying it. Our present knowledge of the cancer problem has shorn it of all doubtful evidence and removed from it statements of questionable character. A discussion of cancer and its nature has formerly been shrouded in considerable mystery, which always created a stumbling block in worthy scientific advance.

For more than a decade the cancer question has been attacked with new vigor and the enormity of study necessary for its full understanding has led to the creation of many research laboratories whose investigators are devoting their lives to its elucidation. Today every opportunity is available to test out theory and opinion by experimental work and there is no longer any excuse for the propagation of hearsay opinion without obtaining

actual evidence for or against the theory. This opportunity alone has been of great value in preventing lay opinion or quack dogma to guide the thought in this problem. Laboratories today welcome suggestions for new thought or new lines of investigation.

The researches up to the present have demonstrated that the cancer problem is a purely biological one, and the studies must be followed and be based upon the principles underlying this science. A knowledge of the cell, its functions and growth is essential and an appreciation of the vagariex of cell life under various influences must not be overlooked. It is truly remarkable how closely the development of tumor stimulates the growth of normal tissues. The work upon the growth of tissue upon artificial media outside the body has given us an understanding of many processes which has heretofore not been possible. The metazoon animal no longer presents itself as a concrete unit, whose parts cannot be dissociated, but each tissue is individual, having laws unto itself.

Interesting as it may be to recite the attempts which have been made to determine the cause and to establish a cure for cancer, I will

discuss the recent work which has been done upon the question of tissue growth. Up unto relatively recently, advances upon this problem have been made chiefly with the aim of establishing a single factor responsible for abnormal tissue proliferation. From this attitude two groups of observations have held our attention. Some recognized the parällel character of tumor cells to the growing cells of the embryo and from this view suggested that the origin and development of malignant tumors was associated with abnormal tissue masses, retaining embryonic characters. The other observers pointed to the similarity of tissue reactions in the adult body following upon injuries and irritants of various kinds. Undoubtedly a morsel of truth is present in each, but with it all, both have their shortcomings in explaining the aberrant and continuous tissue proliferation as seen in tumors. Misplaced embryonic cell masses are truly found in the body associated or not with tumor, and undoubtedly certain masses of cell growth resulting in tumors in the tender years, come from this source. Likewise, as has been pointed out by many, the factor of injury and irritation in later life has a direct bearing in the production of new growth. But in each

again, there is still an unknown quality which in the individuals, of each type of tumor development, permits of the unrestricted growth of the cells. We are constantly struck by the fact that all transitions of tissue reactions following an injury, from the mildest proliferation to inflammation in its various forms and finally advancing with characters of true tumor growth, are to be recognized, and it is not uncommon to meet with such tissue changes in which, from the pathological viewpoint, the greatest difficulty is experienced in determining the proliferative ability of the reacting cells.

From the recent work it would appear that the underlying factor which determines whether the tissues of a particular area will advance in an unrestricted growth to tumor formation is a systemic condition. Ehrlich suggested the same idea in somewhat different form. He believed that the problem of aberrant growth was one determined by the presence or absence of the proper food stuff for these particular cells. It was demonstrated that all tumors cannot be transplanted with equal success to animals. Firstly, transplanted tumor masses will take only in animals of the same species or closely allied families, while again it is found that all animals of a given species will not develop the same transplanted tumor.It would appear that there is something in the constitution of the animal which determines the development of the transplanted tissue.

On the other hand, Bashford viewed the problem from a different angle and believed that the conditions necessary were not systemic but local and that the success of transplant was determined by the response in the stroma in which the inoculation was made. Thus he believed that it was wholly a question of providing the transplant with an adequate and proper nutrition.

Now recently, we have had still further evidence respecting the general features underlying tumor development and these are rather suggestive of there being a constitutional factor determining tumor growth. Slye had two races of mice in one of which there was a family history of the development of spontaneous tumors, while in the other the animals had always been tumor free. By the imbreeding of the tumor mice alone, she found that the incidence of spontaneous tumor was great. These tumors did not always rise in the same organ, and hence we cannot speak of these as inherited tumors. The imbreeding of the non-tumorous animals constantly gave a pure stock of animals which were tumor free. On the other hand, when she cross-bred the tumorous and tumor free animals she found that spontaneous tumors arose in the progeny in the proportion of the Mendelian law of inheritance. She believes, therefore, that there is an inheritable

quality which makes the animals more susceptible or predisposed to tumor development. She furthermore found that there was a determining factor which led to the tumor development at individual sites. This factor was of the nature of an irritant.

If the findings of Slye are corroborated we will find an explanation for the endemic occurrence of tumors amongst animals in certain localities, as well as possibly among families in man determined by imbreeding and cross-breeding of a cancerous stock. You will see, however, that all individuals of a cancerous stock do not develop tumor, but only those who in addition to the predisposition are also influenced by a determining cause present in injury and irritation.

If this inherent quality of the animal body has such an important influence in determining the development of cancer, does this teaching modify the attitude of the practitioner to his patient? As far as we can see, I think not. It may be that if these observations are found to be of sufficient value, eugenic principles may be advocated, but for this to be established as a community law is still in the far

distant future. Of greater importance and easier approach for the physician is the discussion of the active determining factor which leads to tumor production in local areas. There is ample evidence that there are many such factors which have to do with the determination of a neoplasm in a given position. All are familiar with the development of cancer following x-ray burn, a jagged tooth, chronic lupus or syphilitic ulcer, as well as the part that is probably played by ill-fitting corsets and cancer of the breast. There is, in fact, a sufficient evidence that not a few forms of chronic irritation play an important part in actually bringing a cancerous process into being.

Formerly there were many who hoped to find a single and constant active factor underlying every cancerous process, but such ideas have for the most part been dropped. There is no evidence that the same causative agent is at work in the different kinds and types of neoplasms, and from a study of tissue reactions to irritants we have come to appreciate that the effect of many divergent agents is the same. The responses in tissues to chemical and physical causes of disease are often indistinguishable,

and so it is also probably true that a variety of causes can bring about those tissue changes which determine the development of cancer at a particular point.

There are a number of observations which today still give us difficulty of interpretation. In dogs there is a form of lymphosarcoma which, from the clinical and pathological characters is identical with a true malignant growth. But it is found that the condition is contagious and transmitted from one animal to another. Animals may even be experimentally infected with this new growth by the introduction of the tissue juices from the tumor. No living virus has, as yet, been demonstrated, but the observations have strongly suggested that one may be present. Of course, this is not saying that tumors are necessarily of parasitic origin, but only that in this particular case a living virus may play the part of the active factor in determining tumor growth in a susceptible animal.

Observations of a similar nature have also been made by Rous on fowl. He found that not a few tumors, benign and malignant, are readily transplanted from one fowl to another. But more than this, he has also shown that the extracts of crushed tumors of these

animals when inoculated into a new host not uncommonly give rise to another tumor. Curiously enough, the second tumor may be identical with the first, but sometimes he found that the new tumor had taken on new characters or involved a new variety of tissues in the second animal. In carrying out these experiments no tumor cells were permitted to enter the second host and it was even possible to filter the tumor extract through the finest filter candles and still get the same result. Thus Rous was led to speak of a filtrable virus. This virus,however, was much more active when the inoculation was made in conjunction with some sterile inert powder. Here, then, the laboratory studies have suggested a still further factor which has to do with tumor production.

In general, we cannot apply these findings in practice, but it does permit us to appreciate the divergent predisposing and active agents at work in bringing about tumor development. This being true, it furthermore shows that by ordinary means, we are unable to ferret out in each instance the causes that have been at work, animals when inoculated into a new host not uncommonly give rise to another tumor. Curiously enough, the second tumor may be identical with the first, but sometimes he found that the new tumor had taken on new characters or involved a new variety of tissues in the second animal. In carrying out these experiments no tumor cells were permitted to enter the second host and it was even possible to filter the tumor extract through the finest filter candles and still get the same result. Thus Rous was led to speak of a filtrable virus. This virus,however, was much more active when the inoculation was made in conjunction with some sterile inert powder. Here, then, the laboratory studies have suggested a still further factor which has to do with tumor production.

In general, we cannot apply these findings in practice, but it does permit us to appreciate the divergent predisposing and active agents at work in bringing about tumor development. This being true, it furthermore shows that by ordinary means, we are unable to ferret out in each instance the causes that have been at work, so that even in the absence of a knowledge of the cause in a given case we are bound to take the occurrence of every tumor seriously. The presence of a tumorous mass demands an investigation to determine its internal make-up, and today, when that analysis cannot be made by clinical means, necessitates its examination in the laboratory. Of the laboratory methods at our disposal, the microscope still gives us the best results.

THE *STREPTOCOCCUS MUCOSUS*—ITS CAPSULE AND ITS PATHOGENIC PROPERTIES.

By W. L. HOLMAN, Pittsburgh, Pa.

Reprinted from The Journal of Pathology and Bacteriology.
Vol. XIX. (1915).

Journal of Pathology and Bacteriology, Vol. XIX.

THE *STREPTOCOCCUS MUCOSUS*—ITS CAPSULE AND ITS PATHOGENIC PROPERTIES.[1]

By W. L. Holman, *Pittsburgh, Pa.*

From the Pathological Laboratories, University of Pittsburgh.

(Plate XXXVIII.)

Capsules among the streptococci, as among other bacteria, are best developed in the animal body, but they may also be easily shown about organisms grown on different artificial media. The methods that have been devised for their demonstration are far too numerous to be given in this article.

The majority depend upon the fixation by substances, such as acetic, tannic, phosphomolybdic, osmic, and other acids, Zenker's or Mueller's fluids, formalin, and a number of other substances which will precipitate or fix the capsular material and possibly make it more susceptible to the action of certain stains. Gins (1909 [7]) used India ink to make his smears, which were then fixed in concentrated sublimate solution and stained with carbol thionin. The capsules are unstained, but are defined from the stained body of the bacteria by the India ink. Rulison (1910 [21]) applied the India ink after staining and obtained the same general results.

Gozony (1913 [9]) used India ink in the fluid state, and demonstrated capsules around several strains of bacteria of the hæmorrhagic septicæmia group. This method, I have found, gives excellent results, and the extremely simple procedure recommends it as the most practical method yet devised. A drop of India ink properly diluted is put on a slide. A loop of the culture is then thoroughly mixed with it, a cover-glass dropped on, and the specimen examined under the oil immersion lens. The more opaque bodies of the bacteria are easily distinguished from the invisible but clearly defined capsular space.

The capsule of *Streptococcus mucosus*, both from the animal body and from many artificial media, is very easily stained. From old cultures, v. Lingelsheim (1913 [18]) says that capsules are demonstrated with difficulty, and advised the use of the hanging-drop in salt solution, or better in serum. No details are given of the appearance of the capsules, but the author says that the capsule appears much

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[1] Received January 30, 1915.

clearer by the use of 1 per cent. collargol solution, as described by Hamm (1912 [12]). The use of collargol gives the same general picture as does the India ink. The capsular space is not as clear as when India ink is used, and in both methods only a halo is seen and not a definite capsule.

I have found that by growing *Streptococcus mucosus* in serum broth containing lactose, salicin, inulin, or other carbohydrate, fermented by this organism, the development of capsules is remarkably pronounced. A drop from such a culture, put on a slide and a cover-glass placed on it, shows under the microscope that the cocci are surrounded by perfectly distinct and plainly visible capsules (Plate XXXVIII. Fig. 1). This capsule visible in the wet preparation seems peculiar to the *Streptococcus mucosus*, and is not seen from growths of the pneumococcus (Plate XXXVIII. Fig. 2), or the capsulated bacilli of the *B. mucosus capsulatus* group grown in these media. The presence of serum seems necessary, as we have never obtained the same results in plain broth or plain carbohydrate broth. Moreover, it occurs only in carbohydrate serum broth when the carbohydrate is attacked and acid produced. Serum broth cultures of the *Streptococcus mucosus*, to which lactic acid is added in varying amounts, does not render the capsule visible. The gradual development of acid as it occurs during the process of fermentation appears necessary for this development. A capsule is easily demonstrated from blood-agar slants and plain serum by a variety of staining methods, although it is not visible in the unstained wet preparations from these media.

Serum, no doubt, is utilised by the organism in the formation of its capsule, and the acid acts as a slow fixative on this capsular substance, first affecting the capsular membrane and gradually penetrating and altering the whole capsular material.

I have made a number of experiments on the effect of various substances on these visible capsules. A strain of *Streptococcus mucosus* was used which showed, from a lactose serum broth in moist preparation, cocci in pairs and short and long chains. The capsules were distinct and sharply defined. Moist preparations were made and various solutions were applied to the edge of the cover-glass. The effect was noted as these fluids came in contact with the capsulated cocci. Glacial acetic acid caused the immediate disappearance of the capsule. Water, ether, alcohol, glycerin, and 5 per cent. nitric acid had no apparent effect. Formalin made the capsule appear more granular than that in the control specimen, and its edges became more irregular. Zenker's fluid (without acetic acid) showed the outer wall somewhat accentuated. V. Ermengem's flagella stain, No. 3, had a little more effect in emphasising the outer wall. Sodium hydrate, N/20, caused marked swelling of the capsules, and when they were treated with the normal solution they disappeared. Hydrochloric acid, N/20, also brought about swelling, but the outer wall lost its distinctness, while the normal solution showed the capsules unaltered or slightly more marked.

The precipitate from the lactose serum broth culture was twice washed in distilled water and centrifuged. No change was noted in the capsules. After standing overnight in water, at the room temperature, the capsules were still perfectly distinct but decidedly swollen. A half-saturated solution of lime-water was added, thoroughly shaken, and allowed to stand overnight in the laboratory. A few capsules were rather indistinct, but the majority were still clear. After again washing in distilled water there was no notable change. Hydrochloric acid (5 per cent.) was next added, and left in contact for twenty-four hours at 37° C. No change was noted. The capsules were not quite as distinct after washing in distilled water, until the supernatant fluid was neutral to litmus. Nitric acid (5 per cent.) was added to the precipitate from the original; after two washings in water and treatment with the half-saturated lime-water, allowed to stand overnight at 37° C. and examined. The capsules were more distinct and the border accentuated. The precipitate from a fresh culture was twice washed in water and a part boiled in distilled water. No change was seen. Treatment with 4, 6, and 8 per cent. sodium chloride and strong saline solutions had no effect in altering the capsules. Glacial acetic and normal sodium hydrate cleared the emulsion immediately. Washing in 95 per cent. alcohol, thoroughly shaking and centrifugalising, left the capsules unaltered.

The test for sugar by Haines' (1904 [26]) (modified Fehling's) method, after shaking the precipitated culture with dilute hydrochloric acid, gave a negative reaction. After treating with sodium-hydrate solution and adding the Haines' reagent, the blue solution turned to a pale violet. The washed precipitate was boiled with 2·5 per cent. hydrochloric acid, and the capsules disappeared. Haines' test was negative.

Many other tests were made in an endeavour to demonstrate that these capsules contained mucin, but without avail. Staining with Loeffler's methylene-blue did not show the capsules red, as we have observed for *B. anthracis* from the animal body, and which Heim believed was a mucin reaction.

Friedländer (1912 [5]) believed the capsule to be mucin-like, Guarnieri (1912 [10]) that it was an albuminoid (fibroplastin), while Hamm considered it a nucleo-albumin or nucleo-proteid.

In my opinion the composition of the capsule is not the same for all capsulated bacteria.

Fürst (1910 [6]) working with the *B. mucosus capsulatus* group has differentiated two types of capsules—the "Huelle," derived from the surrounding media; and the true capsule, a part of the bacterial cell itself which is differentiated from the true cell plasma. This author used a dilute serum water containing sugar, namely, 1 part of inactivated serum to 9 parts of 0·5–1·0 per cent. aqueous solution of grape sugar. This medium was sterilised at 100° C. for one hour. In this hypotonic solution, Fürst observed the occurrence of granules, followed by the development around the bacilli of gigantic "capsules," or "Huelle." The "Huelle" formed under these circumstances are soluble in alkali; bile and bile salts and 1 per cent. solutions of trypsin digest them. They are only formed in inactivated serum heated over 65° C., and are not seen about non-encapsulated bacteria. They are never formed in active serum, or in serum heated only to 56° C. Their formation, according to this author, depends upon the precipitation of albumin by acids.

There is no doubt that a different type of capsule is dealt with in my observations, as the capsule here described is formed in carbohydrate serum broth, the serum of which has never been inactivated by heat. There are several points of interest, however, in the findings of Fürst, many of which apply equally well to the "Huelle" or the true capsule as I have seen it. Both depend upon the precipitation of the albuminous material: in one case from the surrounding media; in the other, within the capsular membrane. They are obviously also both soluble in alkaline.

I have found the true capsule which is here described constantly present in my *Streptococcus mucosus* strains, both when first isolated and after many months, if the culture is freshly grown in lactose-serum broth. The *Streptococcus mucosus* is a far more resistant organism than is commonly supposed; I have frequently kept it on blood-agar slants for two or three months without transfer. At the end of 104 days, in one strain, after standing at room temperature on blood agar in sealed tubes, the typical watery growth was obtained on fresh blood agar, with greening, followed by a trace of clearing, and later deep browning of the growth. The growth following transfers to lactose-serum broth showed the capsule to be as distinct in the unstained condition as when first isolated.

The technique is to plant the material in serum broth, incubate for about twenty-four hours and plate on the surface of blood agar. The extremely watery sticky green colonies, so characteristic of this organism, are picked to blood-agar slants and directly to the lactose, mannit, salicin, inulin, and other carbohydrate serum broths, or from the blood-agar slant to the other media after the culture has grown. The carbohydrate serum broth is prepared with filtered beef serum, as I have elsewhere described (1914[13]). From the culture in the fermented carbohydrate serum broth a moist preparation is made. The capsules seen are not halos, as is the case with pneumococcus and other capsulated bacteria in this unstained condition, but are distinct and clear cut, and are easily differentiated from the bodies of the cocci. They are seen in 24-hour cultures, becoming more marked after a day or two and persisting for weeks.

Schotmueller (1903[1]) was the first to call the attention of bacteriologists to the *Streptococcus mucosus* as a definitely differentiated organism; while Binaghi (1897 [2]) first recovered and studied this coccus from a guinea-pig dying spontaneously, which showed multiple abscesses in the lungs. The earlier description of capsulated streptococci by Schutz and others is not sufficiently definite to permit the conclusion that they were dealing with this organism.

Bonome (1913 [3]) reported the recovery of this streptococcus from the exudate of a case of cerebrospinal meningitis. Howard and Perkins (1901[14]) isolated an organism which they called *Streptococcus mucosus* from a case of peritonitis. Richardson (1901 [20]) recovered a capsulated coccus, which he named the pseudo-pneumococcus, and which appears to have been identical with the *Streptococcus mucosus* from cases of lobar pneumonia. Schotmueller reported three cases of meningitis following acute otitis media of a comparatively mild type, and one case of pneumonia caused by *Streptococcus mucosus.* He also recovered this organism from cases of peritonitis. Many others have since shown that it is a not uncommon cause of otitis media, and that the prognosis in these cases is not, as a rule, good.

Foss (1909 [4]) reported three cases of abscesses of the brain following acute otitis media caused by the *Streptococcus mucosus,* and gives an excellent review of the literature. Wittmaack (1909 [24]) found this organism in twenty-one out of fifty-five cases of otitis, and observed in these cases an especially prolonged course and a tendency to complications. In forty-three cases of otitis media, Supfle (1909 [23]) found six due to this streptococcus. Kummel (1909 [17]) believed that the *Streptococcus mucosus* had an unusual power to destroy bone, and thus, often after the purulent process had continued for a long time, brought about endocranial conditions. Neumann and Ruttin (1909 [19]) found an abortive course to the purulent process with exacerbations, as characteristic for the *Streptococcus mucosus* otitis. The process is slow, and may, after all acute symptoms have ceased, end in an endocranial complication. Of sixteen cases operated on, nine showed this organism.

Foss believed that the *Streptococcus mucosus* was often mistaken for the pneumococcus. He quotes Lange's five cases of abscess in the temporal lobe following otitis, for which the pneumococcus was given as the cause, as examples of this error. Lange had found that these cases ran a long and tedious course, but that the bone showed nothing but a slight hyperæmia.

From my experience, the finding of *Streptococcus mucosus* in the discharge from the middle ear makes the prognosis unfavourable. The history of a typical case will give the characteristics of many of these *Streptococcus mucosus* infections.

Patient, female, æt. 27. In February 1909 the patient noticed a thin watery discharge from the left ear. There was, at times, considerable pain in the ear. *March* 11. She was admitted to the hospital; improvement followed treatment. *March* 23. A right-sided otitis media developed which was remarkable for the lack of pain. *April* 6. A paracentesis on the right side was performed. The discharge was thin and watery. A culture showed *Streptococcus mucosus.* *April* 22. The patient left hospital with both ears quiescent. *May* 1. A slight discharge from the right ear again developed. The patient was treated daily in the hospital. *May* 16. The patient was readmitted to the hospital with a slight discharge from the right ear and some tenderness over the tip of the mastoid. *May* 20. A paracentesis of the right ear was done. No culture was obtained. *May* 24. The patient complained of soreness behind the eyes. *May* 25. The patient had a frontal headache. *May* 26. The headache was more severe. Temperature, 101° F. at 12 p.m. Patient vomited a slight amount. At 4 p.m. a simple mastoid operation was performed. The antrum was found free. Some granulation tissue was curetted from aditus, and apparently healthy bone was seen everywhere. Probing of the middle ear revealed nothing. Headache was very severe during the night. *May* 27. The patient had a severe headache, retraction of the head, double Kernig, and other signs of meningitis. A papular eruption over the shoulders was noted. *May* 28. A herpetic eruption was seen at the angles of the mouth. A lumbar puncture was done. The fluid showed pus cells and Gram-positive extracellular cocci in pairs and short chains. *May* 30. Cultures from the spinal fluid gave *Streptococcus mucosus.* *May* 31. Death occurred at 8.30 p.m.

An autopsy, on 1st June, showed an acute otitis media ; acute suppurative meningitis ; thrombosis of left lateral sinus (none on the right side) ; and acute septic infection of the Gasserian ganglia.

The *Streptococcus mucosus* may also cause pneumonia. Richardson and Schotmueller, as quoted above, found it in a number of cases. Longcope (1902 [25]) reports one case of an extremely severe and rapidly fatal type following acute lymphatic leukæmia. This author, however, believed his organism, although it showed a close similarity to the *Streptococcus mucosus* of Howard and Perkins, to be a form of *Micrococcus lanceolatus.*

Haines (1914 [11]) found, among seventy-four cultures, isolated from lobar pneumonia, nine which were classified as belonging to this group of capsulated streptococci. He believed that the name *Pneumococcus mucosus* should be adopted for this group instead of *Streptococcus mucosus.* Numerous other reports of this organism in pneumonia are to be found in the literature. I have myself recovered it a number of times in rapidly fatal cases which usually ran an atypical course.

The following case of lobar pneumonia in which the *Streptococcus mucosus* was grown from the blood, four days before death, will illustrate certain of the characteristics of this infection of the lungs.

The patient on entering the hospital had been ill for five days, did not complain of any pain, but felt tired and drowsy. Temperature, 100°·6 F. ; pulse, 100 ; respiration, 36. The onset had not been accompanied by chill or pain. Physical examination showed signs of consolidation over the right upper and middle lobes of the lung. The temperature on the following day was 103° F. ; pulse, 112–132 ; respiration, 40–52. The temperature ran an irregular course, ranging between 100° and 102° F. The day before death it was 100°·4 F. ; pulse, 128 ; respiration, 56. There was slight delirium for two days before death, and patient died after twelve days from the onset of the disease.

Another interesting case was in a young man who developed otitis media and subcutaneous abscesses in the thigh following pneumonia. From both the otitis media and abscess the *Streptococcus mucosus* was isolated. The patient recovered.

There is no doubt that the diseases brought about by this organism are very severe and frequently fatal. The capsule formation so characteristic of this group of organisms is of the greatest interest, from the point of view that it is a protective development against the bactericidal action of the cells and fluids of the body, and its presence may account for some of the peculiar characteristics of these infections. For excellent discussions on the importance of capsular development around bacteria we refer the reader to articles by Gotschlich (1912 [8]), Sauerbeck (1909 [22]), and Kodama (1913 [15]).

I have found the development of a visible capsule a ready and simple means of confirming the differentiation of *Streptococcus mucosus* from pneumococcus, and I would desire others to continue the investigation in order to learn whether it is as constant a finding in their hands as it has been in mine.

CONCLUSIONS.

1. Moist preparation in India ink, as described by Gozony, is the simplest and most practical method for the determination of the presence of capsules on all capsulated bacteria.

2. *Streptococcus mucosus,* grown in lactose serum broth, prepared as we have described, develops a capsule that is plainly visible in the unstained moist preparation.

3. This visible capsule differs from the "Huelle," as described by Fürst.

4. The capsule is probably made visible by the action of its own acids of fermentation on the albuminous material in the capsular substance.

5. The resistance of this capsule to the solvent power of water, alcohol, ether, dilute acids, and other substances is very high. It is rapidly dissolved by normal sodium hydrate and glacial acetic acid.

6. I am unable to demonstrate a glycoprotein in these capsules.

7. *Streptococcus mucosus* has a greater cultural viability than is generally believed.

8. The development of visible capsule in carbohydrate serum broth serves to differentiate the *Streptococcus mucosus* from the pneumococcus.

9. *Streptococcus mucosus* is a frequent cause of otitis media and mastoiditis of a severe or prolonged type, often followed by fatal endocranial complications.

10. *Streptococcus mucosus* is also found as the causative agent in certain atypical forms of pneumonia.

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DESCRIPTION OF PLATE XXXVIII.

Fig. 1.—Moist preparation, unstained and untreated, from 48-hour lactose serum broth culture of *Streptococcus mucosus*, showing distinct capsules, sharply differentiated from the bodies of the cocci. (× 1000.)

Fig. 2.—Similar preparation as in Fig. 1 of pneumococcus. The capsules are not visible, and are represented by faint halos. Stained smears from this culture showed well-stained capsules. (× 1000.)

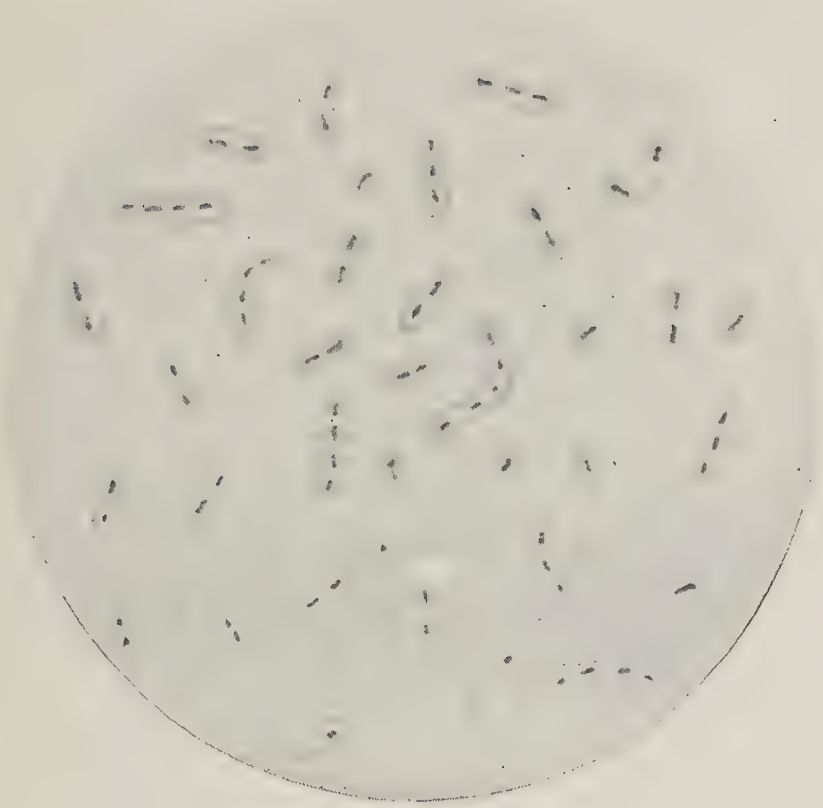

FIG. 1.

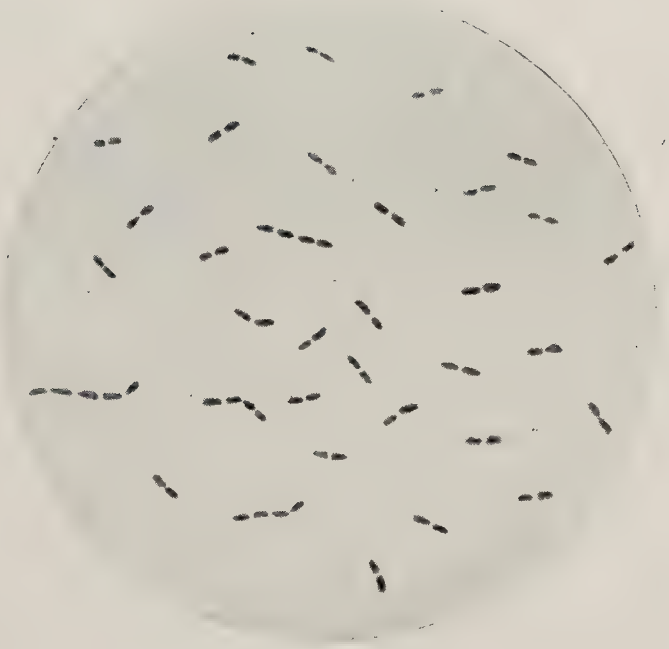

FIG. 2.

SMOKE IN ITS RELATION TO HEALTH,

by

W. L. Holman,

(From the Pathological Laboratories,
University of Pittsburgh).

"Now I see the secret of the making of the best persons.
It is to grow in the open air and to eat and sleep with the earth."

Walt Whitman.

Nothing is more stirring to the city dweller than the realization that out beyond the suburbs are green fields and running brooks where it is possible to "inhale great draughts of space." There is no stronger contrast than that between the close, smoke-laden streets of our industrial cities and the wind-swept places of the plains, the mountains and the sea. While many of us would be glad to indulge in the joys of the country, unfortunately modern life is a city life and we are living in the Industrial Age. The old mill with its slow-turning water wheel, and the modern factory with its roar of machinery- these tell the story.

Water power has been supplanted by steam power. With steam power has come the use of coal, and coal smoke has been pouring from millions of chimneys for a hundred years. It has been and is considered the sign of industrial success. Although it begrimes our buildings, destroys our vegetation, spreads a fine coating of soot over all the interior furnishings of our houses, deprives us of the full brightness of the sun, befouls our clothes

and faces, fills our lungs, and is a general and unmitigated nuisance, yet it is only within the last few years that active measures have been taken to curtail this greatest pollutor of our atmosphere.

Pittsburgh, as a great industrial city, owes its success to the wonderful coal fields in its surroundings. It is only one of many smoky American cities, and when voices are raised against the disagreeable prevalence of this annoyance, it is pointed out that these are the cities that are making the wealth of America.

As early as 1804, General Neville, the Burgess of Pittsburgh at that time, stated in reference to this problem that "the comfort and health, and in some measures the consequence of the place, the peace and harmony of the inhabitants depend upon speedy measures being adopted to remedy the nuisance." That no "speedy measures" have been adopted is evidenced by the fact that over a hundred years have passed, and the smoke is still with us.

The Mellon Institue for Industrial Research has been carrying on a smoke investigation since 1912, and many facts in relation to health have been brought out which should prove interesting to readers of the Journal of the Outdoor Life.

Coal smoke is made up of particles of incompletely burned coal and a number of gases arising from the combustion. It is unnecessary, because properly stoked fires do not produce smoke. The coal wasted in smoke is an economic loss, but

we are living in the stage of extravagant uses of our resources, and the waste continues. The coal as it exists in smoke has been greatly altered by the heat, taking on its sticky,smutty character. These particles of black, greasy coal are being poured into the air in vast quantities,and are deposited more or less slowly on the surroundings. Many hundreds of tons of it are falling yearly in our smoky cities.

First, it is dirty, blackening buildings, window glass and everything with which it comes in contact. It falls on the snow in winter and quickly mars its pure whitness, and in summer the daisies and other flowers have their small faces blackened almost as soon as they have bloosomed. It penetrates our houses and finds its way into linen closets and book cases, and even drifting in through the frames of pictures, will settle under the glass. This penetration which seems so astonishing is due to the expansion of the air when warm, and its contraction on cooling. The alternating expansion and contraction follows every change of temperature, and we have currents of air entering and leaving every closed space. Our tightly shut windows are not barriers against the entrance of very appreciable quantities of soot, but the excess that is noted when windows are open is responsible for an inclination to keep them closed. For this habit, which is very prevalent in smoky cities, and for the bad effects on health which follow this lack of proper ventilation, the smoke nuisance is responsible.

There is, however, a greater influence on the general air of the city due to the frequency of dense fogs in smoke-laden cities, as in the world-famous London fogs. It is interesting that the formations of clouds, mists and fogs depend for their existence on the suspended matter in the air. Warm air, for example, is filled with aqueous vapor, and when the temperature falls, this condenses on the dust particles, just as, when we breathe on cold glass, the moisture in our breath condenses on the glass. Each dust particle becomes surrounded with a tiny envelope of water, and the more numerous the particles, the denser appears the cloud or mist or fog. When the particles become too heavy they fall as rain. Smoke offers innumerable small bodies suitable for the formation of fog.

Now fog has two bad effects on health. First, ir prevents the air of our cities from becoming properly mixed with the fresh ~~outside air~~; and second, it holds irritating gases, which also come from the burning coal, within the breathing zone, and it makes the temperature higher in summer by interfering with the radiation of heat from our streets and buildings, and lower in winter by cutting off the sun's rays. All these conditions have very marked effects on health. Breathing impure air lowers our general resistance, and the irritating gases, by directly acting

on the air passages, make more easy the entrance of bacteria. Acute infections of the nose, throat and lungs are more common in smoky cities than elsewhere and increase during periods of foggy weather.

The second bad effect of fog comes from interference with the sun's rays. Sunlight is our best and most constant germicide. Smoke clouds and fogs allow only the red rays to pass through, as you see it in the familiar red sun. They prevent the passage of the blue and violet rays, and it is these rays that are most active in destroying bacteria. Thus we magnify the chances of infection by lowering our resistance through the breathing of impure and irritating air, and then we interfere with the natural disinfecting action of the sunlight.

The particles of soot do not contain bacteria. On the contrary, soot itself has a definite power of destroying them, but this can only act where the soot is more or less concentrated and is, therefore, relatively unimportant. The dust from streets contains numerous germs, derived from dried sputum, excrement of horses, and a variety of sources. Such dust should not be confused with soot, which as a carrier of bacteria is almost negligible.

Vegatation is an important factor in regulating the composition of the atmosphere. A plant grows through the combined action of sunlight, chlorophyl and moisture on the carbon dioxide in the air. This process is spoken of as on the air passages, make more easy the entrance of bacteria. Acute infections of the nose, throat and lungs are more common in smoky cities than elsewhere and increase during periods of foggy weather.

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Vegetation is an important factor in regulating the composition of the atmosphere. A plant grows through the combined action of sunlight, chlorophyl and moisture on the carbon dioxide in the air. This process is spoken of as photosynthesis. Furthermore, the soot particles often block up the stomata, the little mouths in the leaves by which they breathe, and slow suffocation results. Many of the gases which accompany smoke are also very destructive to the leaves, and dissolved from the air make the rain markedly acid, which has a harmful action on the soil. Today it is a familiar sight to see great trees which have flourished in smokeless days, dead and dying. Oak trees and evergreens are particularly susceptible, but all vegetation is more or less stunted , and sooner or later succumbs to its ill effects.

Every man and woman breathes about two thousand gallons of air in twenty-four hours, and if soot can enter the crevices of our windows and close the tiny mouths of the leaves, it is easy to realize that large quantities of it must enter the human air passages. Much of the soot is stopped in the nose and throat, but nevertheless a great deal enters the lungs and it is the cause of a community disease known as anthracosis. In this disease the lungs become filled with soot particles and are literally as black as a lump of coal. The contrast in that delightful fairy tale, "The Water Babies," between Tom as he came down the chimney and Ellie with her flaxen curls and fair skin, is comparable to the lungs of the city dweller as contrasted with those

of one who breathes the clean air of the country. The body naturally attempts to carry away this foreign material by the channels which serve as drains for the lungs. These drains become clogged, and it is then that the condition becomes dangerous. In pneumonia the lungs are attacked by a particular germ, the pneumococcus and the body strives to overcome it. Where it succeeds, the victory usually takes place in about one week. At this critical point it is necessary, for complete recovery, to clean up the battle ground. The dead and useless material is normally carried away by the channels. If, however, these passages are blocked with soot, the difficulty is increased and failure often results. This is one of the most important reasons for the high death rate from pneumonia in smoky cities. In the case of tuberculosis, the problem is different. Tuberculosis is also caused by a germ, the tubercle bacillus; but this germ acts very slowly, and the defense of the body is to prevent its spreading by walling off the particular part attacked. The mildly irritating action of the soot seems rather to help than to hinder this method of defense. At any rate, the soot has little harmful effect in tuberculosis as compared with acute diseases of the lungs and air passages.

The psychological aspect of the smoke nuisance is also important. Its very presence tends to lower the general tone of a community, and the

depressing effect on children is regrettable. "It is difficult," says C. A. L. Reed,"to imbue the young with a sense of the beautiful, when the beauty itself is bedaubed with soot."

Smoke is an economic waste,a menace to health and a general nuisance. It can be prevented, and will be when people are fully awakened to the extent of the damages it causes, and demand that it be done away with.

City life has advantages and disadvantages. The advantages are well known to us all, but the chief disadvantage is that the general average of health is low. The freshest air that we breathe in a city cannot be compared with country air. This, then, is the great thing to overcome. Smoke with its manifold detrimental effects on the atmosphere must be banished. We must have education on ventilation, open spaces easily available to all the citizens, and in every way do what is humanly possible to overcome the disadvantages and make life in the city equally healthy with that of the country.

Published in the Journal of Outdoor
Life, 1915, vol.xii, no. 5.

PRIMARY MELANO-SARCOMA OF THE ADRENALS

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Reprinted from
The Journal of Medical Research, Volume XXXIII., No. 1
(New Series, Vol. XXVIII., No. 1), pp. 93-106, September, 1915

BOSTON
MASSACHUSETTS
U.S.A.

PRIMARY MELANO-SARCOMA OF THE ADRENALS.*

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As a rule the pigmented tumors arise in the skin, choroid coat of the eye, or less frequently, in the meninges. Other organs, however, have also been mentioned as possible sources, and in the literature not a few examples of this can be found. In the works of Borst and of Ribbert on tumor, the skin, choroid, and pia mater are the only regions mentioned as primary foci. Mallory[14] gives the same locations. There are, however, a number of other regions capable of giving rise to this tumor, as may be observed by the reports of Wittig, Duval, and others. Borst[3] considers the esophagus, gall-bladder, and rectum as possible primary sites, while the liver, ovary, uterus, bladder, urethra, and breast have been mentioned by other authors. It is not unlikely that many of the tumors occurring in the rectum are but extensions from the pigmented area of the anal orifice, and, therefore, should be classed as having an origin from the skin. We have had a case of this type recently where the growth had extended from the anus into the rectum, producing extensive pigmented metastases. Tuczek has also referred to this, but further held that the ganglionic nerve cells, which contain melanin, may be the cells from which some pigmented tumors arise and thus account for some of the very unusual situations in which this tumor is found.

Melano-sarcomata of these infrequent sources are very interesting and should be brought forward, not only on account of their rare occurrence, but also to add new facts which may have a direct bearing on the interpretation of the type of the cells which comprise them. For such reasons we are reporting a case of primary melano-sarcoma, arising in the adrenal glands. The tumor was bilateral and almost

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* Received for publication May 30, 1915.

symmetrical. A complete autopsy was performed and a most exhaustive search failed to demonstrate any primary neoplasm in the skin, choroid, or meninges. The following protocol is taken from the Mercy Hospital Laboratory Records:

P. K., aged 48 years, admitted April 19, 1910, died April 20, 1910. Service of Dr. T. S. Arbuthnot. The autopsy was done one hour after death by Dr. Oskar Klotz. No history was available as the patient was comatose, and no information could be obtained from any friends. He had been picked up from the street by the police, who believed him to be intoxicated. As he lived only a few hours after admission to the hospital, a careful clinical examination was impossible. The finding of albumen in the urine, associated with the comatose condition, strongly suggested the clinical diagnosis of uremia.

AUTOPSY. — The body was that of a very tall and well-developed man whose skin surfaces had a pale, leaden appearance. Scattered in the deep subcutaneous tissues of the trunk and upper extremity were many movable nodules, averaging two centimeters in diameter. These nodules had a bluish appearance through the skin, but on section were black. None of them were attached to the epidermis. In the subcutaneous fat and recti muscles of the abdominal wall more than thirty of these black nodules were found. No mole could be found upon the skin, nor did any of the tumor masses present at the surface.

A pigmented tumor one centimeter in diameter was found in each parietal bone, and innumerable nodules were present in the brain substance and pons and medulla. A single small nodule appeared in the falx cerebri, but none were found in the leptomeninges. The eyes and optic nerves were carefully examined and found to be free from tumor. The accessory structures of the brain were normal.

In the thorax a pigmented tumor was found in a mediastinal gland and a single small mass the size of a marble was present in the right lung. The heart showed the presence of multiple small pigmented tumors in the musculature of the right auricle and ventricle and in the left auricle. A mural thrombus attached to the wall of the left ventricle was found projecting towards the aortic valve.

On opening the abdomen, the cavity was found to contain about one hundred cubic centimeters of recent blood, still in a fluid state. The abdominal viscera were everywhere coated with thin blood. Examination of the abdomen showed scattered nodules beneath the peritoneum of the abdominal wall, tissues of the mesentery, liver, bowel, and other viscera. Three large masses of tumor were also found, one on each side directly above the kidney in the region of the adrenals. Each of these masses was the size of an orange. The third mass was lying posteriorly in the mid-line near the cardia of the stomach and attached to the left lobe of the liver. This mass was as large as a grape fruit, and its anterior surface was adherent to the stomach along the lesser curvature. On its posterior surface the mass showed a tear in its capsule and the tumor tissue was also torn. From these parts the peritoneal bleeding had its origin. Elsewhere, the tumor, which was intensely black, was covered by a thin capsule. The great omentum contained a number of nodules the size of cherries. Many of the glands in the mesentery were invaded by black growths.

Along the greater curvature of the stomach were seen two nodules raised above the general mucosal surface and having a crater-like center. This central crater was dark in color and represented tumor mass undergoing ulceration. Four small tumor ulcerations from 1 to 1.5 centimeters were seen in the duodenum. The tumor masses appeared to arise in the submucosa. Throughout the jejunum and, in fact, the whole course of the small intestine, there were innumerable (hundreds) raised pigmented nodules in the mucosa with ulcerating surfaces. Sometimes these nodules formed projecting masses like polypi with narrow pedicles. These masses were frequent in the ileum, but were also common in the cecum, some being present in the colon and sigmoid. There were two types of nodules in the intestines. The one type being shallow, crater-like ulcerating nodules which lay mainly in the submucosa. The other type formed pedunculated masses which arose from the mucosa and which hung like grapes from the mucosal wall.

Tumor masses were seen through the capsule of the liver. On section of the liver a number of encapsulated black tumor masses were observed. Several of the glands at the hilus also contained tumor tissue. The large central tumor mass, which has previously been described, measured 12 x 9 x 8 centimeters. It lay for the most part in the liver and obliterated the Spigelian lobe. This mass was very soft, black in color, somewhat lobulated and had ruptured. It was encapsulated, and rested posteriorly upon the vertebra. The gall bladder showed six small pedunculated black tumor masses at the fundus. The bile ducts were clear.

Several small encapsulated black masses, about one centimeter in diameter, were seen in the pancreas, and also in the loose connective tissue and lymph glands about the organ. A single nodule was present in the spleen.

Each kidney was of about the usual size and was surrounded by a thick layer of fat, in which were studded many small black tumors. There were no tumor masses in the kidney substance proper and both organs were normal in appearance. Over the upper pole of the left kidney and in the region of the adrenal was a large and intensely black-colored tumor mass, 10 x 8 x 4 centimeters. On section the tumor was more or less lobulated and its tissues were soft and friable. It was surrounded by a thin capsule and sharply separated from the kidney substance. No remains of adrenal substance could be found. From the renal vein, a vessel passed over the face of the tumor and entered it at the apex. Over the right kidney, in the region of the right adrenal, was another tumor 10 x 9 x 4 centimeters. This tumor mass was similar in every way to the other on the left side. The right adrenal gland could not be recognized in the tumor mass.

A black tumor mass the size of a walnut was seen projecting into the cavity from the wall of the bladder at the fundus. The genital organs, rectum, and anus were without change.

Microscopical. Adrenal tumor mass. — There was no evidence of any normal adrenal tissue, nor did the arrangement of the tumor mass, in any way, suggest adrenal structure. The tumor was made up of a very dense cellular tissue having no special arrangement of its cells. There was a very slight stroma carrying moderately-dilated and thin-walled blood vessels. In the perivascular lymph spaces, collections of lymphoid, plasma and a few polymorphonuclear leucocytes were to be seen. The cells forming the tumor were variable in size and shape. Round, oval, and spindle forms were seen, the round forms slightly predominating. The spindle cell, at times, showed fairly long protoplasmic cell processes. Some of the round forms were small, while again others were quite large and not infrequently showed multiple nuclei. The nuclei generally were round, or oval and vesicular. The nuclei varied also in size and often appeared in multiple groups. In some cells it was impossible to make out the nucleus on account of a very large amount of coarse brown granular pigment, which more or less filled the whole cell. The pigment content of the tumor cells was very variable. Most of the cells contained some, but a few cells were quite free from it. Where the pigment was abundant, only the shape of the cell could be made out, as the protoplasm and nucleus were hidden by the heavy brown granules. Nuclear figures were fairly numerous throughout the tumor. There were no ganglionic nerve cells present, nor were there any cells which, in any way, resembled the adrenal cortical cells. The pigment did not show the presence of iron with the Nishimura test.

The tissues of the organs of the body were also examined and the tumor masses of the lungs, duodenum, spleen, and pancreas resembled the structure as above described. The great variation in the shape and size of the cells was striking, but the difference in the quantity of the pigment also varied to a marked degree. Round, spindle, and spider-shaped cells were the most common variety found in the tumor masses of different regions, but it was not uncommon to find large syncytial pigmented masses scattered through the tumor tissue.

A careful histological examination was made of the eyes and optic nerves and nowhere was tumor found in them. Furthermore, there was an entire absence of tumor cells in the kidney, but a melanotic pigment was easily demonstrated in the cells of the convoluted tubules.

The main autopsy findings are summed up in the anatomical diagnosis. Primary bilateral melano-sarcoma of the adrenals, with secondary tumors widely distributed in all organs, save the kidneys; hemoperitoneum from rupture of tumor mass; tumorous ulceration of bowel; mural thrombus of heart.

To briefly summarize the protocol we find a primary bilateral melano-sarcoma of the adrenal with extensive metastases in a man of forty-eight years. The skin, choroid of eye, and meninges were uninvolved in tumor growth. Microscopically the tumor differed in no way from the usual melano-sarcoma which arises in the skin or in the choroid.

The bilateral nature of the tumor is, indeed, interesting from several points of view. The symmetrical appearance was striking. The tumor masses on either side were almost equal in size and shape. The shape of the tumors, roughly triangular, bore a likeness to the normal adrenal, and the relation of the tumor to the kidney was that of the normal adrenal gland. The bilateral involvement we can regard in no other light than two primary foci. This strongly suggests to us that in this case the factor of congenital misplacement of cells capable of producing melanin pigment must be considered. Both of paired organs are not infrequently involved in a similar pathological process. The congenital cystic kidney, ovarian dermoids, and papillomatous cysts are such examples. In view of this it is not improbable that the adrenals may also at times show bilateral congenital conditions. By congenital condition in this case we do not mean to infer that the tumor itself was congenital, but in view of its cellular structure one is led to believe that previous to the tumor formation there was a congenital aberration of the pigment-containing cells, the so-called chromatophores. We have numerous examples of this in the pigmented nevi of the skin, so that it is not improbable that a congenital increase or malplacement of chromatophore cells may also occur in the adrenal, and lead later in life to the development of a malignant tumor.

Probably the most interesting finding in the case was the pale, leaden appearance of the skin associated with complete destruction of the adrenals. Why did we not have pigmentation of the skin as is seen in Addison's disease? From the man's history it is known that he was virtually a tramp and, therefore, was exposed almost continually to the open air, which would give ample opportunity for the skin to become pigmented. Lack of skin pigmentation is sometimes noted in Addison's disease, but it can usually be demonstrated by putting the patient in the sunlight to activate oxidation of the colorless pre-pigment substances. This explanation certainly does not apply to our case. The pigmentation of the skin in Addison's disease is regarded at the present time as due to a melanin pigment. An accumulation of this pigment is brought about by the destruction of the adrenal with partial or complete loss of its function. Following this there is an alteration in a series of chemical events by which there is a tendency to accumulate pigment material. The production of melanin is regarded by v. Furth as the result of two processes. By autolysis, the protein molecule is broken up and the aromatic compounds as tryosine are acted upon by the oxidase, tyrosinase, with the development of a pigment, known as melanin. In this connection it is of interest to know that adrenalin is chemically closely related to tyrosine, and experiments (Kastle[10]) moreover, have shown that adrenalin can, by the action of an oxidase, produce a pigment. Oxidizing enzymes are numerous and are present in many tissues. Meirowsky has proved that an oxidase in the skin can by acting on adrenalin produce pigment. Similarly of great interest to us is the work of Neuberg, who isolated from a melanotic tumor of the adrenal an oxidase, which was also capable of producing a pigment by acting on adrenalin. These findings tend to show that where certain derivatives of the protein molecule come in contact with an oxidase, pigmentation is the result. Under normal conditions of metabolism this process does not occur on account of the influence exerted by the adrenal glands, particularly the medullary portion. When, however, the adrenals are interfered with, by the pathological changes in the organ, so that they do not normally carry out their functions, pigmentation develops, particularly on the exposed parts. The adrenals were totally destroyed in our case, yet there was no pigmentation; in fact, there was a very marked pallor. Total destruction of the adrenals without pigmentation of the skin has been known to occur. Sometimes the pigmentation can be demonstrated in these cases by exposing the patients to sunlight and open air. Others believe that the chromaffine cells, associated with the sympathetic ganglia elsewhere, can carry on the function of the adrenal medulla, and hence no symptoms of Addison's disease develop. Dr. Klotz has advanced an hypothesis for this odd finding. The amount of melanin pigment in the primary tumors and the metastases was very excessive. It is possible that in the production of this pigment by the tumor cells all of the essential constituents, namely the protein derivatives and the oxidases were, so to speak, used up, and were not available in the skin in a proportion sufficient to produce pigmentation. To put it briefly, in other words, the tumor cells contained all of the pigment that was produced. To say what factor was absent in the skin, whether the oxidases or the protein derivatives, we, of course, do not attempt to suggest, but it does seem highly probable that the active tumor cells contain protein derivatives in a more available state for the action of the tyrosinase than does the skin. One point may be cited as possibly adding an argument in favor of this contention, that tumor cells are prone to undergo autolysis. In relation to this is the generally accepted theory of von Furth, of melanin production, in which he states that autolysis of the cell with liberation of the aromatic radicles of the protein molecule is the first step in the formation of the pigment melanin.

There are very few similar cases in the literature. Davidsohn[5] refers to a case reported by him as the first primary melano-sarcoma of the adrenal with metastases that has been recognized.

The case is so like our own that we think it wise to cite the more important points. The tumor occurred in a man of 58 years. Widely distributed dark pigment growths was the principal post-mortem finding. No primary focus was found in the skin or eye. Both adrenals were enlarged, each measuring 8 x 4 centimeters. The adrenals on section still showed evidences of normal tissue, but the greater part was replaced by a large pigmented tumor mass. The tumor was made up of cells of various shapes and sizes and contained pigment in fine or coarse granules. Some cells were free from pigment. He, however, compared the tumor growth to some of the adrenal structures. Its arrangement was similar to the zona fasiculata, and moreover, the cells contained a fat-staining substance similar to that in the adrenal cells. In arrangement and form of the cells there was also a likeness to the medulla of the adrenal. Further, he added an apparently convincing fact that he had demonstrated adrenalin in the extracts of the tumor metastases.

In the discussion of the tumor Davidsohn refers to four somewhat similar cases in the literature, two in Orth's Text Book of Pathology, a case reported in the Prager Med. Wochenschr., and finally one from Marchand's Laboratory in Leipzig. All of these appear to him of doubtful adrenal origin, the first two giving insufficient proof, while Marchand[12] himself, in the discussion of Davidsohn's paper, said that the case reported from his laboratory was not clearly shown to be a primary melano-sarcoma of the adrenal, as two retrobulbar masses were present which he regarded as more likely to be the primary focus. Davidsohn concludes that his tumor definitely arose from the adrenal, and the demonstration of adrenalin in the mesenteric lymph node metastasis was, to him, a very important point in proof of this.

Goldzieher[6] has reported an identical case in a man twenty-nine years of age, showing a bilateral pigmented tumor of the adrenals with extensive metastases.

The adrenals measured right, 9 x 6 x 4 centimeters, left, 7 x 4.5 x 3.5 centimeters. The tumor cells were typical of melano-sarcoma. In the left adrenal there was still a considerable amount of normal-looking substance. He has very different ideas concerning the interpretation of some of the points of his case. To begin with, he regards the right adrenal as the primary site, and the left adrenal tumor merely a secondary growth. Further, he does not consider Davidsohn's observations on the presence of adrenalin correct. He was unable to confirm it in his case. Lastly, in view of Lucksch's [11] work on benign melanomata of the adrenal cortex, he concluded that it was from these adrenal cortical cells that his tumor arose.

Another newer case, and also one which bears a resemblance to our own, is that of Tuczek.[19]

We shall refer to some of the points in his well-worked-up report. The case was a bilateral primary melanoma of the adrenal without metastases in a female of 47 years. In structure the tumor was composed of variously-shaped cells containing large and small granules of pigment. Some of the cells were quite free from pigment. Tuczek enters into the question of the nature of the pigment and the origin of the cells quite thoroughly. He comes to the conclusion that the pigment in his case was a true melanin, and not a lipochrome as is normally found in the adrenal cortical cells. He therefore does not consider the adrenal cortical cells as playing any part in the origin of the tumor. There are, however, two other types of cells in the adrenal which contain melanin, and from these cells the tumor may have arisen. In the loose, connective tissue about the adrenal, both in man and in other animals, he has found chromatophore cells containing melanin, while again in the ganglionic cells of the medulla, as has been previously shown, a true melanin also is found. He leans to the second of these two possibilities, but still considers that an origin from the chromatophore cells is also very probable.

In our case the outstanding feature was that we were dealing with a typical melano-sarcoma. It differed in no way, microscopically, from similar tumors which arise in the skin or in the choroid. After an exhaustive search of the skin and choroid as well as by ruling out the other possible sites, we concluded that the tumor was primary in the adrenal gland and bilateral in its origin.

Arising, therefore, in the adrenal, the question naturally was asked even in spite of the unusual pigmented character of the growth, whether this tumor, microscopically, would show any similarity to the hypernephromata. In this regard our findings were negative.

Lucksch,[11] in an article on benign melanoma of the adrenals, refers to three cases and further suggests that a close search will probably reveal many more. These tumors were small, brownish growths, lying in the cortical substance and also infringing on the medulla. They were formed by cortical cells and contained a dark pigment which Lucksch considered as melanin. All of his cases occurred in adults over fifty years. Schmorl has also spoken of small melanomata of the adrenal cortex and holds that they are by no means infrequent. Goldzieher regards these benign melanomata as having a very important role in the production later on of malignant melanotic tumors. He believes his case had such an origin.

From the medulla of the adrenal another type of tumor arises which, according to Herxheimer,[8] can be classified in the following way: (a) neuroblastoma, (b) ganglioneuroma, (c) paraganglioma. But from the microscopic description of the cases given and from my own, there is no doubt that these tumors cannot fall under any of these classes.

In his conclusions Tuczek regards the presence of melanin pigment in the ganglionic cells as ground for the theory that this tumor may arise from altered neuroepithelium which enters into the formation of the sympathetic system in the medulla of the adrenal. Aschoff has also pointed this out in the discussion on Goldzieher's paper. Goldzieher, on the other hand, contends that too much stress must not be laid on the type of pigment as the differentiating factor of a tumor. Hueck[9] was not able to demonstrate true melanin in the adrenal cortical cells, but adds that it is present in the ganglionic cells. Tuczek has confirmed these findings. The pigment in the tumor cells of our case was similar in every way to that seen in other melanomata. Ordinary stains were of no value in differentiating this pigment. The pigment did not stain with Sudan III., although in the tumor cells an occasional fine, reddish-stained granule was to be noted. This, however, is not unusual and can be demonstrated in practically any tumor. We do not, therefore, lay any stress on this finding. The Nishimura's iron reaction was negative. The pigment, therefore, as far as we can say from histological grounds, is melanin.

The important question now arises as to the origin of the tumor in the adrenal. In the first place the almost symmetrical appearance of the tumor, lying as it did in the normal position of the adrenals, cannot, we think, be regarded other than of bilateral primary origin. In shape the tumor was roughly triangular, not unlike the adrenal. We accept Ribbert's[16] theory that melanomata arise from cells which have the power of producing melanin, the so-called chromatophore cells or melanoblasts. These cells, we believe, are mesoblastic in origin. Tuczek has shown that occasional chromatophore cells are to be found in the loose connective tissue about the adrenal gland, and Aschoff[1] has also repeated this statement.

We cannot convince ourselves that the ganglionic cells played any part whatever in the tumor formation. If the tumor had arisen from these cells, it is but logical to expect on microscopic examination some suggestion of a growth of nervous origin. This was entirely wanting and we feel justified in ruling it out of consideration. The fact that ganglionic cells do contain melanin cannot be regarded as an indication that a melanotic tumor must come from that source. For like reasons we consider the adrenal cortical cells as unassociated with our tumor tissue. The tumor bore no resemblance to the adrenal cortical cells, either in appearance or arrangement. Further, our tumor was pigmented by melanin, and according to Hueck, Tuczek, and our own observations, this pigment does not occur in the adrenal cortical cells. The pigment in the adrenal cortical cells is a lipochrome and not a melanin.

The only cellular origin left is the chromatophore, and it is from this type of cell, we believe, the tumor arose. Tuczek has found chromatophore cells in the loose connective tissue about the adrenals in normal cases of man and other animals. After searching many adrenals, I have been unable to satisfy myself of such cells, either in the tissues about the adrenal or in the adrenal itself. However, we know that chromatophore cells are not at all times pigmented, and, therefore, might be easily overlooked. Broniatowski[4] has shown this in his studies on the chromatophore cells of the pia mater. Ribbert[16] also refers to the same fact in his writings on chromatophore cells. The negative findings, therefore, in the study of adrenals, do not, by any means, influence our opinion that these cells are not present, and by overgrowth may produce a very malignant tumor. According to Tuczek the chromatophore cells arise from the neuroepithelium. We, however, agree with those who believe that they are of the mesoblastic origin.

This question of origin of chromatophore cells we do not wish to discuss at any length, as it has been taken up more fully in the papers referring especially to that point. There are, however, several types of pigmented tumors involving the nervous system which show, when taken collectively, a common factor in their construction, namely the existence of an undue development of chromatophore cells. In the first group are the cases reported by Oberndorfer,[15] Grahl,[7] and myself,[13] where there was a diffuse pigmentation of the skin and central nervous system in infants. The skin lesions were simple nevi pigmentosi, while the meninges and brain showed a diffuse increase of pigmented and non-pigmented nevus cells. The conditions were of congenital origin and were essentially benign. Grahl and Oberndorfer regarded the epidermis and neuroepithelium as the tissue from which the pigmented tissues arose. I held they were mesoblastic in origin. In the second group are the melano-sarcomato, arising from the chromatophore cells in the pia mater. Cases are reported by Schopper,[18] Sternberg, and others. In the last group we may class the melanomata of the adrenal which we have referred to in this paper. We think Davidsohn, Goldzieher, Tuczek, and our own case may be grouped in one class. We believe that they arose from chromatophore cells lying in the medulla of the adrenal. As we have previously mentioned, we have been unable to demonstrate typical chromatophore cells in the normal adrenal gland, still, this is by no means a conclusive argument against their presence, and in some cases, producing malignant tumors. Moreover, Tuczek has demonstrated chromatophore cells in the loose tissue about the normal adrenal, although he does not regard these as the cells from which his tumor arose. Here again the origin of the chromatophore cells from neuroepithelium comes up, to which Tuczek attributes his tumor. We, however, cannot confirm his evidence. Davidsohn and Goldzieher both held the cortical cells responsible for the tumor growth. In view of the description of their tumors we cannot believe other than that they were identical with our own, and arose from the same type of cell.

CONCLUSIONS.

1. Primary bilateral melano-sarcoma of the adrenal gland may occasionally occur.
2. Its origin in the adrenal is from chromatophore cells, which are probably congenitally aberrant.
3. The pigment of the tumor, which is melanin, differs from the normal pigment of the adrenal cortical cells, which is a lipochrome.
4. Total destruction of the adrenals by a pigmented malignant tumor may occur without any pigmentation being present in the skin.

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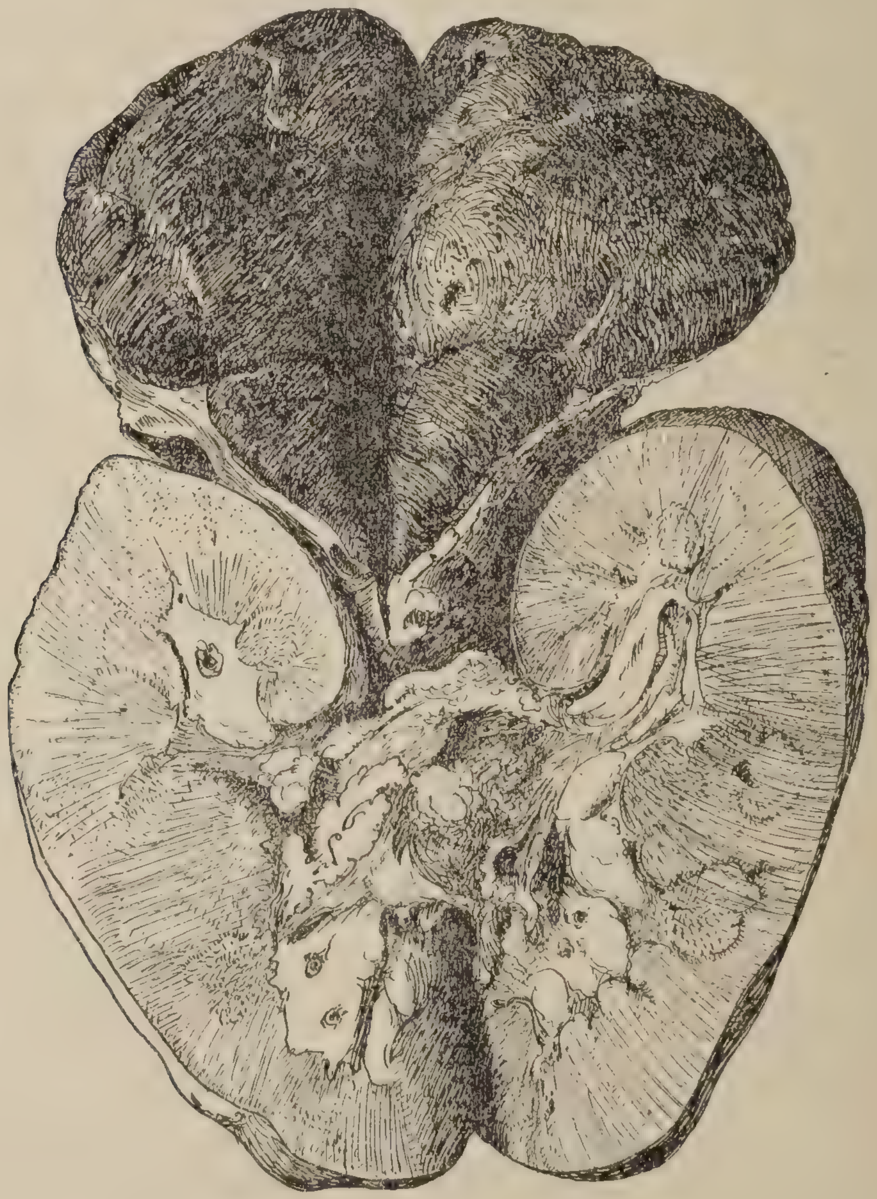

Fig. 1. — Primary melano-sarcoma of adrenal.

THE SPLITTING OF THE ELASTIC FIBERS IN ARTERIES

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Reprinted from
THE JOURNAL OF MEDICAL RESEARCH, VOLUME XXXII., No. 3
(New Series, Vol. XXVII., No. 3), pp. 377-390, July, 1915

BOSTON
MASSACHUSETTS
U.S.A.

THE SPLITTING OF THE ELASTIC FIBERS IN ARTERIES.*

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The changes to which the elastic fibers in arteries are subject form a series of events and interesting problems which have occupied the attention of many investigators. The importance of the part played by these changes in arteriosclerosis has been warmly supported, particularly by Jores, who is of the opinion that splitting of the internal elastic lamina with a hyperplasia of smooth muscle constitutes true arteriosclerosis. Weissmann, Neumann and Manchot observed a granular degeneration of the elastica in the early stage of arteriosclerosis and aneurysm. Dmitrijeff concluded that in arteriosclerosis there was both disappearance and new growth of elastic tissue. The former, essentially by a degeneration, seen in the early stages of the disease is primarily marked by changes in tingibility, followed by morphological alteration and eventually necrosis. He states further that the newly formed elastica, like some other young tissues, possesses less resistance to noxious influences and hence yields readily before excessive pressure or deleterious bodies. Thoma's experiments have proved that the fibrosed artery presents a higher degree of resistance coupled with a lessened elasticity. Likewise Luck found in diseases with disturbed nutrition, as in cancer, tuberculosis, and sepsis, a weakening of the vessel wall with diminished elasticity. This weakening continues until endarteritic processes appear, when, with the development of new connective tissue in the artery the resistance increases and the vessel is not so easily dilated. Luntz found that the vessels of cats poisoned with phosphorus, lead, and mercury during the subacute stages were less resistant to a distending force and did not show gross pathological change. The progressive tissue changes

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* Received for publication March 22, 1915.

noted by Aschoff and Foster consist in an increase in the elastic fibers, which they believe result from an increased pressure as well as wear and tear on the arterial wall. Faber states that in arteriosclerosis all arteries from the smallest to the largest may become calcified and that the internal elastic lamina and media are attacked most severely. He further says that the calcification of arteries preferably begins in the elastic tissue and that mechanical force must be the underlying cause of this as well as of fatty degeneration.

We wish to confine our study of the elastic fibers more particularly to the changes occurring in the internal elastic lamina of the peripheral arteries and endeavor to explain the nature of these alterations and the relations which they bear to sclerotic diseases of the vessel wall.

The elastic tissue in the peripheral arteries occurs principally between the intima and media, forming the so-called internal elastic lamina. There are, however, other elastic fibers which are found in the media in the form of fine threads and also an external layer, the external elastic lamina. The latter lies between the media and adventitia. The most important of all these elastic structures is the internal elastic membrane. Normally it is seen in cross section as a highly refractile band running around the artery and is usually thrown into wavy folds due to the contraction of the vessel wall and also in part to its own inherent contractile power when muscle inhibition is lost. The band is of moderate width and stands out in bold relief with well defined edges in unstained specimens. When the artery is cut longitudinally the elastic tissue is seen to be in the form of a sheet having small oval openings. It surrounds the artery in the form of a tube, being a definite coat in itself. The amount of elastic tissue varies in the different arteries according to the function of the vessel (Foster, Aschoff). In the aorta it is particularly abundant and increases in quantity until the thirty-fifth year when, after a period of quiescence, it increases in relative amount as the muscle tissue diminishes in absolute quantity.

The elastic tissue does not stain well with the ordinary tissue stains but requires special methods. With Weigert's elastic tissue stain it is colored a deep purplish black, the whole fiber apparently taking the stain equally well. Verhoeff's elastic tissue stain shows the fibers a deep black, uniformly and sharply differentiating them from the surrounding tissue. Although elastic tissue is preferably demonstrated by these special stains we have observed that it can also be well shown by several other methods. Arteries which have been preserved for quite a time in formalin show the elastic tissue well stained by phosphotungstic acid hematoxylin. Here the fibers are seen as sharp deep blue bands which appear to have an outer darker covering from which the inner fiber is sharply defined. Mallory's aniline blue stain for connective tissue colors the elastic fibers a bright orange and here again a similar outer portion is differentiated from the central fiber. Sections stained by Weigert's and then treated with a phosphomolybdic acid Orange G of the same strength as in Mallory's aniline blue stain show that the inner fibers often prefer the Orange G and the external elastin coat takes the Weigert's. Sections stained with van Gieson's show the fiber staining dark with the first and an outer coat colored bright red. This last method gives interesting results in split and degenerating fibers and will be considered later. Recently Harris has pointed out that elastic fibers appear to be made up of an inner and an outer coat. However, he was not able to make out a definite limiting zone between these two parts. Mall has shown that elastic fibers are composed of two distinct substances, an outer delicate sheath which does not stain in magenta and an interior substance which is intensely colored by this stain. The inner substance is highly refractile. With the staining methods which we have employed we have seen this feature constantly, especially with the van Gieson stain. This appearance is also quite clear with aniline blue and phosphotungstic acid hematoxylin. We have noted that these dyes did not always stain all of the elastic tissue with equal intensity and sometimes not at all. To us it appeared that the healthy tissue took the stain more intensely. This has also been referred to by Harris and our results coincide with his, both having used the same mordant as recommended by Mallory. With this difference in the staining quality of the inner and outer parts of the elastic fiber it would appear that they are either chemically different or exist in a physically different state.

Although Weigert's elastic stain almost always acts uniformly on elastic fibers, we have, nevertheless, noted that the outer part of the fiber takes the stain more intensely. Goodall in his description of the elastica interna in the vessels of the nulliparous uterus notes that each fiber is a cylinder which, by the ordinary Weigert's stain, has a black contour and a pale nile-green center.

The elastic tissue in the arteries which shows pathological change most frequently and most markedly is the internal elastic membrane. Although other of the elastic fibers throughout the wall show splitting, the ultimate effect upon the vessel is small compared with the splitting of the internal elastic membrane. The causes of the splitting have been so much in dispute that we believe we may offer the results of our observations, some of which materially assist in understanding the underlying principles of the process. At the very outset we must point out the fallacy of attempting to lay down a hard and fast rule governing a process in which there appear to be so many variations. This in all probability is the very point upon which hinge so much confusion and misunderstanding of the theories of arteriosclerosis.

Concerning splitting of the elastic fibers, Jores believes that the condition is brought about by a mechanical forcing apart of the fibers due to the overgrowth of the smooth muscle cells. He says that a muscle cell hyperplasia always precedes the splitting of the fibers and that these cells are consequently found lying between the fibers. It is true that muscle cells are at times found between the split fibers, but we have failed to verify the statement that only muscle cells are found in these spaces. Very often it is quite difficult to definitely recognize the character of a cell where the cell protoplasm is poorly or indistinctly stained and infinitely more difficult to name a cell from the appearance of a nucleus without its surrounding cytoplasm and cell membrane. We have, however, observed excellent examples of splitting of the internal elastic membrane where fibroblasts and endothelial cells could be identified and further we have studied specimens showing splitting of the internal elastic lamina where an inflammatory exudate lay between the split fibers. In some of our cases this inflammatory process was of an acute nature, while in others it was of a more chronic type, showing lymphocytes and endothelial-like cells described by Klotz in his study of nodular thickenings about the intercostal arteries. In these cases all grades of splitting were seen, from the fine granulation of the edge of the fiber to a wide separation of the fiber into strands with the inflammatory cells lying between them. Fine granulation and notching of the inner border of the elastica interna was noted in the arteries of the brain in acute septic meningitis. Here the small arteries showed a marked swelling and edema of the intima with an infiltration of inflammatory cells which did not go beyond the limiting elastic membrane. The media was free from exudate while the inflammation was again encountered in the adventitia. This reaction in the inner and outer coats of the vessel wall coincides with the statement of Klotz that an inflammatory reaction may occur simultaneously in the intima and adventitia without affecting the media. It further illustrates the point made by Aschoff that notching of the inner border of the fiber occurred when the inner wall of the vessel was acted upon by irritating substances in the blood.

From our observations it was quite evident that changes in the elastic tissues do occur independently of a weakened media. Again in the walls of vessels where the reaction was more acute and further advanced, we found the elastic fibers split with the inflammatory cells lying between them. We have observed this condition in acute septic meningitis, septic thrombosis following rheumatism, and in the arteries bordering on inflammatory foci notably in the lung in acute lobar and unresolved pneumonias. We have further examined the peripheral arteries from cases of diphtheria, scarlet fever, septicemia, typhoid fever, pneumonia, chorea, and in all of them have observed varying degrees of change in the elastic layer associated with inflammatory processes in the intima. These cases ranged in age from five to forty years. The products of an acute inflammatory reaction were not present in all, but each showed some elements or reaction indicating a tissue response to an irritant. The change in the elastic tissue was evidenced by a granulation and splitting of the fibers, the diffusion of elastin-staining material between split fibers and the difference in the tingibility of the fibers.

Koester in speaking of mesarteritis believed that the muscle and elastic fibers of the media were much affected by the chronic inflammation. Furthermore, Wiesel was of the opinion that rupture of the elastic fibers in typhoid fever was due to a degeneration and not to increased tension, and that later the elastica disappeared and was replaced by granules and small masses of aggregated particles. Bory, who studied the reaction of the elastic tissue to irritants, concluded that elastin disappeared quickly by a process of fermentation when near an inflammatory focus. He thought elastin was not a living substance but that it was brought to the connective tissue and not manufactured by the connective tissue cells. He compared it to fibrin from the blood. Klotz and Saltykow, both of whom produced identical arterial lesions experimentally, although using different microörganisms, noted splitting of the internal elastic lamina.

In a recent study of "Nodular endarteritis of the aorta about the intercostal arteries," Klotz says: "In our preparations the splitting of the elastic lamina and the early development of a fatty degeneration in the cells of the immediate vicinity, though appearing a little later than the first changes in the inner connective tissue layer, are a progressive accompaniment of the inflammatory process. The development of fine elastic fibrils in the intermediate zone between the intima and media and which later extend into each of these layers is also an early reaction in these lesions."

Manouelian, by injecting rabbits and monkeys intravenously with filtrates, dead or devitalized emulsions or living cultures of the staphylococcus found that the chief lesion in the arterial wall consisted in a degeneration of the elastic and muscle fibers. He found a new formation of elastic fibers from the elastica interna, which loses the power for its elective stain and becomes fragmented.

From the altered reactions of the elastic tissue in these cases it would appear that some chemical change had taken place. In any event there is definite evidence of a "melting down" or dissolution of the elastic substance so altering the fibers that they are able to unravel. This in all probability is brought about by the presence of deleterious substances acting upon them, and not by mechanical means.

Splitting of the elastic fibers occurs in the arteries of individuals independently of their age, as we have found this condition in childhood and adolescence, a time when stress and strain or wear and tear could not be a prominent factor and when senile degenerations were still far distant.

That this condition is permanent when once brought about appears evident. It always remains as a split fiber and, when the lesion is repaired, fibroblasts, endothelial cells, and at times muscle cells are found between the strands. Again there may be no cellular structure between the strands but only a fixed homogeneous elastin-staining material, without cells or fibers. However, this substance appears to be closely associated with hyaline deposits as, in a combination of Weigert's and van Gieson's stains, it is colored bright red by the fuchsin. Manouelian noted that in monkeys the degenerated elastic fibers were replaced by collagen.

The alterations seen in elastic fibers of arteries are very varied and the earliest sign of such changes is indicated by deviations in the reaction of the elastic substance to the special stains. The so-called splitting of elastic fibers appears to be closely associated with a progressive change in the structure of the fiber which can be demonstrated by the staining reactions. As the outcome, the fibers are found split longitudinally, transversely, frayed out into many fine threads, or show a moth-eaten granular appearance.

Sometimes well stained fibers are seen which suddenly become much wider and nodular and stain much less intensely. These again narrow down and the fiber again stains as before. Closer examination of these areas shows a blurred homogeneous-looking base in which fine dark threads as well as a varying number of dark irregular granules are seen running parallel to the long axis of the fiber. The threads and granules appear to stain with equal intensity. At times fibers broaden out and show a heavily stained thread on either side, with a pale-staining homogeneous material between them. Other deeply stained fibers are noted to lose this quality and continue apparently unchanged in width for some distance and again take on its deeper staining qualities. Fibers are seen where the main thread seems to divide, continue thus for a distance and then reunite. Such divided fibers do not always stain with equal intensity, one may be quite uniform in width and staining qualities while the other is swollen, blurred, and less distinct. Some fibers appear to stain entirely on one side with a less stained portion included in the general outline. The granulation of fibers is quite often arranged in rows which, as they become more closely arranged, run together to form a fiber with granular characters. From these fibers and running to other fibers are bands of quite definite outline which, in general, stain faintly, but have fine delicate threads incorporated in them. These threads are most frequently seen on the edge of each band and arise from the point of bifurcation of the main fiber. Sharply staining fibers frequently end suddenly, but a faint outline of them trails off into a diffuse homogeneous ground substance in which it disappears. Hilbert found that the ends of split elastic fibers were often connected by unstained threads or by granular and broken fibers.

The granular staining of otherwise intact fibers is very often seen. These granules appear along the edges as sharp projections sometimes on one or the other side but, in general, on the side next to the irritating substances. This is best shown in areas where an inflammatory exudate is lying between split fibers. Again the granulation may be seen on both sides of the fiber nearest the inner surface of the vessel where it is in relation to an inflammatory process.

A homogeneous, faintly-staining ground substance is frequently seen between split fibers and acts as a matrix for the granules. Frequently this substance does not stain at all and is arranged in the form of bands between the split fibers. A material similar in all respects may be seen lying on the inner side of the elastic layers where they come close to the intimal surface. The internal elastic lamina lying in close relation to the blood stream is seen to diverge and become covered by this peculiar material. When examined in sections stained to demonstrate nuclear structures, these are found absent. This appearance is particularly true in vessels showing splitting of the internal elastic lamina. Sections stained by using a combination of Weigert's elastic tissue stain, Weigert's iron hematoxylin, and van Gieson's stain show very interesting pictures. The elastic tissue stains in all shades, accepting both the Weigert's and van Gieson's and in places what appear to be combinations of the two. Some of the fibers are stained quite black, while others are yellowish black. This appearance was particularly found in the case of split fibers. Along the edges of the fibers there was a bright red band easily distinguished from the surrounding tissue. This same red substance could be seen in the form of bands between split fibers and also between the ends of transversely split fibers. It was also found close to the surface at those places where the fibers receded from the lumen. Within these red bands were often observed deeply stained fine lines or fine granules making up the thread. Where deeply stained fibers became swollen, this bright red substance was incorporated in the fiber with the fragmented portions of the dark-staining material. Such fibers frequently assumed their normal appearance at some distance from these foci.

It would appear from the comparison of sections stained by the two methods that where the elastic substance stains only faintly it has an avidity for the fuchsin in the van Gieson's stain. From this one may assume that the elastic fiber has undergone an internal change which has altered its nature. We do not believe that this change is an entire loss of identity but rather a chemical one altering certain of the constituents of the ground substance which, under normal conditions, binds the internal fibrils into a consolidated whole. It appears to represent the end result of a chemical decomposition starting in normal elastic tissue.

The splitting of the elastic fibers is seen in a variety of types. The one most marked is that of longitudinal splitting. In this type a fiber may divide and form two fibers which may again join or break up into further strands and form quite a mesh-work. The intricate mesh-work of split or new formed fibers may again reunite into a single fiber. Split fibers may run long distances before reuniting. A common change in split fibers is granulation, the granules becoming smaller, the farther they are from the main fiber or, remaining of uniform size, again become compact and join the main trunk. Split fibers quite frequently stop in brush-like ends made up of minute threads which trail off into the surrounding tissue and are lost. Split fibers often end in homogeneous diffuse areas which appear swollen and blurred. Splitting transversely is quite frequently observed and can occur at any angle. The break may be clean or occupied by fine granules and threads or again it may only be apparent, with a faintly-staining homogeneous ground substance between the blunt and deeply-staining ends. At times the elastic fibers appear swollen and coiled on themselves and when split look like the fraying of a rope.

Sections stained with Sudan III. show that the fibers are very frequently infiltrated with a very fine granular material, which is so abundant that this Sudan staining material makes up the contour of the fiber. In many places it begins along the borders of fibers in the form of fine granular dots, occurring more frequently on the inner border of the fiber or on fibers exhibiting granular edges. It does not follow, however, that degenerations as indicated by other staining reactions will be fatty in nature because, even in the same field, fibers showing fatty degeneration and elastoid degeneration may be seen. Again in the same degenerated area of a fiber the fatty material is found interspersed with masses of elastin-staining material. From our observations we cannot support the view of Faber, Virchow, Davidsohn, and others that the changes occurring in elastic tissue are most frequently of a fatty and calcareous nature. On the other hand, we feel that there are changes which precede the fatty and calcareous states. These are of such a nature that the elastic tissue gradually acquires a special affinity for fatty substances. This is analogous to the condition pointed out by Klotz in hyaline and amyloid degenerations, which also have a special liking for fatty substances. It would thus appear that hyaline, amyloid, and elastin material are closely allied. In sections cut on the flat the Sudan-staining material is sometimes seen as a wash, the elastic fibers appearing as almost homogeneous orange-staining streaks (Klotz). Associated with fatty degeneration of the elastic fibers calcareous degeneration is quite commonly seen. It occurs as a granular crystalline material in the fibers.

The alterations found in the intima associated with splitting of the internal elastic membrane may be either proliferative or degenerative. This is in accordance with the findings of Klotz, Heisel, Faber, Hansen, and Simnitsky in their observations upon the arterial system of individuals who had suffered acute infections. In the most acute stages of the inflammation the intima is swollen, puffy, and the intimal cells are quite widely separated. All of the cells of the intima are much swollen and quite granular looking, while a great many of them show only faintly-staining nuclei and an ill-defined outline. Along with this there is a marked infiltration of inflammatory cells consisting for the most part of polymorphonuclear leucocytes with only an occasional lymphocyte and plasma cell. The remarkable feature of this infiltration is that it is almost always confined to the intima and does not go beyond the internal elastic lamina into the medial tissues. However, in some sections a few inflammatory cells are seen on the outer side of the elastic layer bordering on the muscle tissue of the media. Again, on the other hand, we wish to be clearly understood that an inflammatory infiltration may occur in the intima and adventitia without the slightest sign of involvement of the media. We are firmly convinced that this inflammation is primary in the intima and support the opinion of Klotz that "the cellular exudate found in the intima appears to arise by a direct migration of the wandering cells from the surface of the artery." As a part of the intimal reaction we find the elastica interna notched and granular along the inner border where it is in relation to the inflammatory process of the intima.

Where the process is particularly acute and incited under different conditions, as in septic thrombosis, we find destruction of the intima with the inflammatory cells lying between the split and degenerated elastic fibers and extending throughout the vessel wall. An artery may be primarily affected by such an acute inflammatory reaction or the inflammation may be found associated with a previously existing condition in the intimal tissues. We have noted both of these conditions in different arteries of the same individual. Following such reactions in the intima the process of repair consists of a connective tissue proliferation. Gerlach in a report upon juvenile gangrene noted that the internal elastic lamina was split in the vessels affected and denied the presence of true arteriosclerosis. He observed that the vascular changes consisted of a connective tissue proliferation of the intima of a true inflammatory origin.

In other arteries along with splitting of the internal elastic lamina there are found degenerative processes in the intima consisting of all grades from simple fatty degeneration of the intimal cells to the stage of atheroma. Along with these changes there is frequently an infiltration of lymphocytes and a few plasma cells together with the presence of large endothelial-like cells containing fat. Although the internal elastic lamina also shows fatty change in many cases, there is often evidence of a fatty change when the elastica is free and separated from the area of degeneration by cells containing definite nuclei.

When the inflammation is acute and there is evidence of a "melting down" of tissue a fine granular fat is seen in the polynuclear leucocytes, endothelial-like cells, and other cells of the affected part. The endothelial cells are in greater number in the subacute stages, increasing in number as the acute stage subsides. In specimens showing old areas of fatty degeneration there is also evidence of more recent alteration accompanying the new acute inflammation. From this we are inclined to believe that many areas of fatty degeneration have their origin in such an inflammatory reaction.

For the above discussion, only cases of definite inflammatory origin were selected with the special intent of ascertaining the effect of inflammation on the elastic tissue in vessels. It would be fallacious to conclude that alterations in the elastic fibers occur only when associated with such a reaction. This is obvious because there are other factors which cannot be classed with inflammation. Granted that such may be the case we have offered evidence that inflammation was the factor operative in our cases. In its action, it and its agent were responsible for the changes which occurred. These in their turn would leave their imprint permanently upon the vessel wall.

CONCLUSIONS. — Elastic fibers are made up of an inner fibrillar material and an outer substance which acts as a sheath. These two substances are probably of a somewhat different chemical composition as indicated by their unequal reactions to stains.

An inflammatory reaction may occur simultaneously but independently in the intima and adventitia without affecting the media. The deleterious substances of this reaction, acting upon the outer sheath of the elastic fiber, cause a diffusion of it and thus free the fibrillar mass. The bundle of fibrils split into multiple threads while the inflammatory products migrate between them.

Further, these factors also act upon the fibrillar substance itself, causing granulation of this material and diffusion into the outer sheath. We do not agree with the statement of Jores that a muscle cell hyperplasia always precedes the splitting of elastic fibers.

The changes found in the intima associated with splitting of the elastic fibers may be either poliferative or degenerative, depending upon the severity of the inflammatory reaction. The elastic fibers are markedly affected in the early stages of degeneration. This degeneration is demonstrated very clearly by the reaction of the fiber to the stain and is only occasionally fatty in character.

When the internal elastic lamina splits it remains permanently in this state. This phenomenon must be looked upon as one of the factors tending toward arteriosclerosis, and not as constituting arteriosclerosis in itself.

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THE JOURNAL OF MEDICAL RESEARCH, Vol. XXXII., No. 3, July, 1915.

FIBRO-ADENOMA OF THE CILIARY BODY.

By A. J. BRUECKEN M.D., Pittsburgh, Pa.

(From the Pathological Laboratories, University of Pittsburgh.)

(*With one illustration on Text-Plate XIV.*)

Reprinted from the Archives of Ophthalmology, Vol. xliv., No. 5, 1915.

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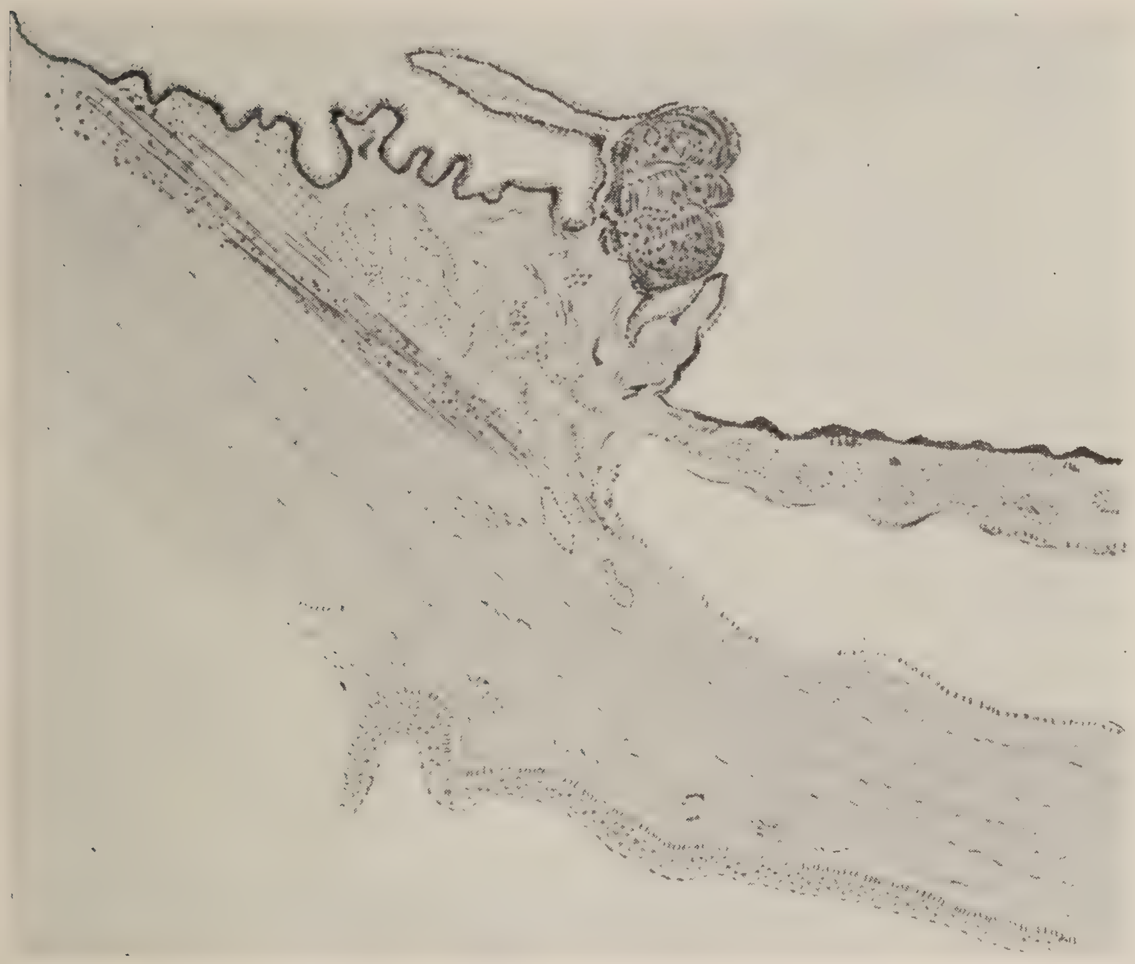
DURING the routine microscopical examination of pathological specimens for diagnosis, a small tumor-like mass was found in the ciliary body of an eye which in the gross showed no evidence of its presence. The eye had been removed from a man of 63 years. The microscopic picture of the eye confirmed the macroscopic observations, save that the small new growth could not be detected by the naked eye. The materials were referred to me by Dr. Klotz for further study.

The history of the case was as follows: The patient worked all his life in a steel mill, and occasionally had pieces of flying steel get into his eyes. These were removed and he noticed no after-results. There was no history of conjunctivitis except at the time the foreign bodies were present. Six years ago the patient noticed a small white enlargement of the skin at the inner canthus of the left eye. This increased rapidly in size. After several months the mass was burned away by a physician. Three months later the inner canthus became inflamed and progressively worse. About eight months ago he had another operation performed, but the incision did not heal. Then he developed a sloughing cavity on the left side of the nose, apparently involving the eye. The eye was removed by enucleation. No tissue from this growth was received in the laboratory.

The eyeball externally was of normal size and appearance, but quite flaccid. The cornea and iris showed no change. The pupil was contracted and measured *2mm* in diameter. After prolonged fixation in ten per cent. formalin the globe was opened. The chambers and their contents

ILLUSTRATING DR. BRUECKEN'S ARTICLE ON "FIBRO-ADENOMA OF THE CILIARY BODY."



Fibro-Adenoma of Ciliary Body.

appeared normal. The crystalline lens was in situ, but fell away on the slightest manipulation of the eyeball. It measured 1*cm* in diameter and 0.4*cm* in thickness. Its consistency was very firm and on section the central portion was very hard. The iris, retina, choroid, and sclera showed nothing of special note and the ciliary body was well developed. No evidence of a nodule was seen in the ciliary body.

Microscopically there was seen in the anterior portion of the ciliary body, situated in the apical part of the ciliary process, a small irregular round or oval tumor mass, not over 0.75*mm* in diameter, staining purplish with hæmatoxylin-eosin. There was a remote resemblance to an intracanalicular fibro-adenoma of the breast, but aside from this it appeared quite unique. The ciliary plications were well marked, though there was no evidence on cross-section of the so-called "gland lumina," the recesses between the ciliary folds within the inner fibrous layer of the ciliary body and running in an equatorial direction.

The tumor mass occupied a position in the ciliary body directly opposite the equator of the lens and only one large ciliary elevation or fold intervened between it and the root of the iris. Unlike the tumor-like masses described by Alt, this mass was embedded in the surface of the fibrous layer of the ciliary body, forming a very low projection into the interior of the eyeball. Here on its inner surface it presented an appearance of having been deprived of the covering of the pars ciliaris retinæ, and, as indicated above, it apparently bounded the canal of Petit externally. However, it showed along this surface a definite layer of epithelial cells which in the anterior part were intact, but in the posterior part were somewhat broken. This covering represented the inner unpigmented cells of the pars ciliaris retinæ, which elsewhere was well defined into its two layers, but had an abrupt ending of the outer pigmented epithelial layer at both ends of the tumor mass. It is possible that the projecting portion of the tumor was broken away, and what was taken for the unpigmented cell layer of the pars ciliaris retinæ may have been one of the many epithelial cell layers present in the tumor. This was supported by the fact that those pigment cells on its surface at the anterior end were isolated, ill-defined, and had their pigment dispersed. The inner fibrous layer of the ciliary body was of apparently normal thickness, but the ciliary muscle fibers were abundant and the circular fibers of Müller were well represented. The connective tissue in some of the plications, like that of the tumor, stained quite deeply and appeared dense and hyaline in character. Elsewhere the connective tissue of the plications was finely fibrillated and showed relatively large and thin-walled blood-vessels. There was no change in the neighborhood of the tumor mass where, it may be noted, the blood-vessels were fairly numerous. About the circulus major, which was represented by two vessels, one behind the other, there was a large number of mononuclear leucocytes. Numerous lamellar and pigmented connective-tissue cells were present throughout, but were particularly abundant in the anterior portion of the ciliary body.

The tumor mass itself consisted of a sharply defined body made up of aggregations of epithelial cells embedded in an abundant homogeneous, vacuolated, and quite acellular substance which stained uniformly pale blue with hæmatoxylin-eosin and in all respects resembled the denser connective tissue noted in some of the ciliary folds. With higher power one could make out a fine fibrillation of this substance which was similar to the tissue of the ciliary folds. This substance, therefore, which represented a type of connective tissue, constituted by far the greater part of the mass.

Alt described four tumors which were similar to the above case. He refers to the stroma as a "coagulated amorphous substance" and found some compressed and flattened cells in the tumor appearing like spindles of connective tissue or myxomatous cells. It was difficult in some instances to differentiate the connective-tissue nuclei from the epithelial-cell nuclei. The connective-tissue cell nuclei were either very irregular or elongated and of large size, but not as large as those of the epithelial cells. Sometimes the connective-tissue cell nuclei were distinctly nodular in appearance; nevertheless, all these forms were also noted in the connective tissue of the ciliary body generally.

With van Gieson's stain the stroma was less conspicuous on account of the brownish color of the epithelial protoplasm which was found to occupy a larger portion of the tumor mass than was supposed. Thorough search for blood-vessels in the stroma showed their entire absence, although there were a fair number in the surrounding tissue. The epithelial cells showed large deep blue-staining oval, round, or polygonal nuclei with very poorly defined cell bodies. The protoplasm was of a clear homogeneous nature and showed no evidence of pigment granules except the marginal cells of the tumor mass. The latter formed a single almost continuous flattened epithelial layer on the inner surface of the rounded cup-shaped impression of the fibrous layer of the ciliary body in which the tumor resided, and it was this layer which so clearly demarcated the mass from the latter. At one place, however, this was not so, and here there was seen an inward extension of connective tissue from the fibrous layer of the ciliary body, which appeared to represent a plication with the usual covering, as is seen on the inner aspect of the ciliary body and a direct continuity between it and the connective-tissue stroma of the mass. Under low power, on account of this sharply defined limiting pigmented cell membrane, the appearance was not unlike an invagination and proliferation of the unpigmented cells of the pars ciliaris retinæ. The surrounding ciliary connective tissue immediately adjoining the tumor growth showed no change or relation to the tumor mass other than that mentioned. The protoplasm of the epithelial cells in the new formation seemed to merge insensibly into the surrounding tumor stroma even when stained by van Gieson's, in which it differed from the epithelium of the ciliary body. The arrangement of the epithelial cells was quite diverse: only a few formed tubules, while most were arranged in single or double layers which did not appear like glandular structures. The cells were often distorted, and the general haphazard disposition of all of the epithelial elements indicated a rather passive nature on their part, with no evidence of a proliferative response. Nevertheless, there was in most instances a more or less well defined contour and continuity of the epithelial cells, and in view of the receding character of the new formation with the excess of fibrous tissue there seemed to be little doubt that the tumor mass represented an epithelial inclusion with but little growth of the epithelial elements. The process may represent a primarily loosened and folded membrane of the pars ciliaris retinæ as Alt suggested, but in the present state the mass mainly consists of a fibrous-tissue increase. However, it is also possible that the fibrous-tissue increase of the folds was primary and the inclusion of the epithelial cells in the mass of hyaline connective tissue was only an associated condition.

In the absence of definite landmarks, such as gland lumina and cell membranes, one could not determine the exact position of the nucleus within each cell, but at the margins of the mass the nuclei appeared to be placed centrally. The nuclei, although they stained deeply, were not pyknotic and mitotic figures were not observed.

A section through the nodule at a different level showed the stroma more deeply stained with a well-marked reticulated structure, while the epithelial cells were decidedly darker. In this section, which showed several indentations in the margin resembling infoldings of the epithelium, there was also an abundance of stroma. The indentations in the margins may represent spaces between the adjoining infolding membrane of the pars ciliaris retinæ, as already suggested. The peculiar nature of the connective tissue of the fibrous layer of the ciliary body, as observed by Dr. Klotz, not only in this case but in inflammatory conditions such as glaucoma, is noteworthy. Notwithstanding the fact that the fibrous layer of the ciliary body is normally quite thick, there appears to be, in these instances, a definite increase and hyaline transformation of the stroma.

In his article on "Intraocular Epithelial New-Formations," Alt considers several possible explanations for such tumor masses, namely: hyperplasia of the palisade cells of the pars ciliaris retinæ, analogous to hyperplasia of cells in the pigment epithelium of the iris, ciliary body, and choroid; their relation to carcinoma, described by previous writers; their possible inflammatory character; their relation to Treacher Collins's so-called "glands of the ciliary body"; and, as above mentioned, the possibility of the development of the process in the loosened and folded membrane of the pars ciliaris retinæ. He speaks of hyperplasia of the pigmented cells of the pars ciliaris retinæ during plastic cystitis as follows: "The whole layer appears very much thickened and grows into the cyclitic membrane in an irregular way. We, however, also observe frequently a more typical kind of proliferation of the cells of the uveal layer in the shape of cylindrical tubes which grow into the cyclitic membrane and give off branches. In longitudinal and transverse sections these tubes appear like the glandulæ tubulosæ or the epithelial cylinders of an epithelioma. The cells of these tubes are either free of pigment or pigmented. Their shape and arrangement with their branches have given some authors (Schiess-Gemuseus) the idea that they are blood-vessels whose walls are filled with pigment."

As can be seen from the description of our tumor mass none of the above would appear to apply to it, for it showed no association with a cyclitic membrane, was not pigmented, showed sharp localization, presented no definite tubular arrangement of its epithelial cells, and lastly, the absence of blood-vessels, or any suggestion of these, was one of its prominent features.

But Alt does describe in this, and more fully in a previous article, a number of new-formations which from his illustrations and descriptions appear very similar to the one we have found. They differ in their location in the ciliary process and in the extent of their projection into the interior of the eyeball, but are alike in the involvement of but one ciliary process, the localized and segregated nature, the absence of pigment, the nature of the epithelial cells and stroma, and in the absence of blood-vessels. Interesting too, the period of life in which they are found is the same. The first four examples that Alt describes were observed in both eyes of a man who died from pneumonia, an eye removed for sarcoma of the conjunctiva, and an eye affected with panophthalmitis. In none of the cases had there been any symptoms or signs referable to the neoplasms, and their finding was wholly accidental, as was our specimen. Naturally this was due to their small size; still Alt's masses were larger than ours.

Alt called these tumors adenoma of the ciliary body in view of their gland-like tubular structure, but he tries to make clear that he does not necessarily believe the ciliary "pegs" to be true glands as Treacher Collins claims.

Previous to Alt, similar tumors were described by Pergens, Badal and Lagrange, and Michel under different names as "adenoma," "primary carcinoma," and "mixed endothelial and epithelial carcinoma" of ciliary body respectively, while Hanke described another such tumor under the name of "an epithelial tumor of the ciliary body." He mentions some such masses as "primary melanotic tumor," "primary melanotic glandular carcinoma," "primary epithelial tumor of the ciliary body," "glioma of the pars ciliaris retinæ," and other names given by various authors. He concludes that there can no longer be any doubt that epithelial new-formations are found to spring from the two epithelial layers of the ciliary body and processes and in rare cases from the pigment epithelium of the choroid as well as the iris.

Unfortunately, because of the small size of the nodule precluding the possibility of obtaining any further sections, and on account of the fixation in formalin, any further special stains for the stroma in our case could not be made.

The tumor mass was too compact and too deeply placed to represent retraction of the anterior layer of the suspensor ligament of the lens with inclusions of the pars ciliaris retinæ. There was obviously some proliferation of the epithelial cells, as the surface area represented by them was much greater than normal. In the absence of any evidence of cyclitis or cyclitic membrane one must recognize the neoplastic nature of the mass. The relation to a fibromyxomatous tumor in view of the repeated slight traumatism of foreign bodies would be interesting, but one could make out no definite evidence of a true myxomatous change of the fibrous tissue though in part its reactions were such.

Could it be that the growth represented an overgrowth of epithelium with the development of a very dense stroma in some of the ciliary folds? That is, could it not be that these new-formations represented simple papillomatous growths with no other etiology than irritation? It is possible that, through excessive efforts to accommodate in hyperopic eyes, with elasticity of the lens lessened, the pars ciliaris retinæ becomes greatly folded, and in places where there is unequal muscular contraction may even become firmly compressed, with consequent hyperplasia of the cells of the area involved. This view is supported by the early and progressive hyperopia in the history of our case. On the other hand, it may be that the injury from numerous foreign bodies, of which the patient speaks, points to traumatism as a possible factor.

What we have attempted to emphasize is the importance of the stroma in our case pointing to a passive character on the part of the epithelial structure.

MEDICAL MEN IN LITERATURE,

by

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Medical men in literature. The subject brings up a host of names; only a few of the more prominent can be mentioned. Some were "literateurs" almost to the exclusion of their medical profession. Others accomplished good work in both lines, combining successfully a busy practice and genuine literary production. Smollett having practiced very little and Goldsmith practically not at all. Of the real literary physicians, Sir Thomas Brown, who died in 1682, was an early instance. Dr. John Brown, who died in 1882, having lived through almost the entire Victorian period, and Dr. S. Weir Mitchell, who died only a short time since are more modern examples of the busy physician who found time to produce literary work of merit. Oliver Wendell Holmes and Dr. W. M. Osler belong to this group.

Such men as those mentioned would doubtless have produced literature, regardless of their profession; but the humanizing influences of their associations in practice, and the unrivalled opportunities for observation of life, often of the seamy side, which are so

numerous for a doctor, must have been important factors in their literary work. These factors, too,must have been seconded by keenness of insight and acute powers of observation, faculties which a physician of necessity develops to a considerable degree.

Ordinary medical writings, all more or less technical, can hardly be called literature; nor is there much chance that work of this type could have been followed by the writings which cause the names of these men to live.

In the works of the writers mentioned, without exception, the style is remarkable. Its clarity, directness and conciseness are features which may possibly be considered as natural results of a physician's habits of thought. Grace and elegance and other refinements were the result of the individual's associations, education, and genius.

The general tone of the works of various medical "literateurs" varies widely. Smollett is gay, light, witty, even coarse and almost vulgar, and at times decidedly broad. With this, he combines a cynical, satirical vein; and as reading matter, merely for recreation, he is irresistible. Dr. John Brown is genial, easy going, scholarly in a delightful, dabbling way, and down right sentimental. A rare thing for a Scotchman and practically always committed to paper. It must be granted, too, that this Dr. Brown lived in a sentimental age. But through the work

of these, as well as the others mentioned, there runs a vein of deep, great-hearted humanity, treating human foibles and failings kindly, and palpably affected by the nobler qualities of human character. The religious note varies, though from occasional glimpses one gets the impression of a deep and lasting faith--perhaps a rather surprising discovery. Dr. Osler, S. Weir Mitchell and Oliver Wendell Holmes rarely mention it, though when touched it becomes a deep and sincere note. In Smollett and Goldsmith, it is a negligible factor. Dr. John Brown had a true and simple faith well fitting with his other delightful, though nowpossibly-- and regrettably-- old fashioned character and writings. Sir Thomas Brown, however, whose works comprise "Religio Medici," "Christian Morals" and "Urn Burial" and some others less notable, was deeply religious in an orthodox but remarkably sane and philosophical way. His writings are altogether along religious and philosophical lines; and written, as they were, at the close of a long and active life-- (Christian Morals he completed when over eighty years of age)-- they contain the essence of his experiences. These books are wonderful. In both theme and literary construction, they stand as an English classic of highest rank. Osler includes Sir Thomas Brown in his excellent list of the ten books that every doctor should

own and read diligently. The others may be of interest. They are: The Old and New Testaments; Shakespeare; Montaigne's Writings; Plutarchs Lives; Marcus Aurelius; Epictetus; Don Quixote; Emerson; and Oliver Wendell Holmes. Osler, aside from his extensive medical writings, excels as an essayist, though usually on topics related to medicine. Dr. S. Weir Mitchell's delightful novels everyone has read. "Hugh Wynn" and "The Red City" are probably the most popular, and deservedly so, being perfect examples of the historical novel, with a complete reconstruction of the manners and customs, the topography and architecture and skillfully drawn noted characters of early Philadelphia. They are written in the purer English of that day, free from all traces of our modern speech.

Smollett's novels are entirely contemporary with him in subject matter, and are written in an excellent style, and a satirical vein. Smollett was born in Scotland in 1721. His father, though of a good family, was disinherited of the little he would have been entitled to as a"younger son", because of an unsuitable marriage. So that Smollett was born and raised in moderate circumstances. He received a good education, and was apprenticed to a surgeon in Glasgow at about the age of seventeen. At eighteen, he started for London, carrying in his pocket a very bad tragedy; for he had already

begun to write. He had a rather stormy time in the big city, but finally, through the influence of friends, was articled as a ship surgeon's assistant, probably his last adventure as a doctor. The expedition was to Jamaica and was apparently rather exciting, judging by incidents recounted in "Roderick Random"; for this book deals with a similar trip and the writer undoubtedly got much material on that voyage. In Jamaica, too, Smollett married. His wife was the daughter of a wealthy plantation owner. His return to London was the real starting point of his literary career. His novels include Peregrine Pickle, Roderick Random, Ferdinand Count Fathom and Humphrey Clinker. Beside these, he wrote a History of England, and edited several magazines. His quarrels, fights and law suits were numerous and show well his great pugnacity and irritability of disposition. A curious thing is the heroes of all his books have been blessed by their creator with characters so similar to his own, in which his own attributes, together with a most unchilvarous bluntness predominate, and are off-set by only one really heroic characteristic-- a dauntless courage. This they are all endowed with in such abundance that no obstacle can prevent the furthering of the plot; not, at least, so far as the hero is concerned. The following conversation, overheard and reported in a letter by a character in Humphrey Clinker, hits off well the prevalent quacker of Smollett's time. (p.23,--H. C.).

Dr. John Brown, the kindly old Edinburgh physician and charming essayist, published two volumes of essays and short papers of various kinds, all more or less closely related to Edinburgh. Some were sketches and appreciations. The preface to his published works is one of the most interesting parts of the book. He makes a number of good points in it. He speaks of his great love and respect for his preceptor, Dr. Syme, the surgeon, he of "Syme's amputation." The incident of his apprenticeship to Syme must have been an important one to both men; for while it was Brown's entrance to medicine, Syme, then a young man, purchased his first gig with Brown's apprentice fee, "And", Brown adds, "I got the first ride in it." **Early** in the preface, Brown makes a strong appeal for the return to the "old days" of broad culture, in the finer things, for physicians. Next, as is natural to a practitioner, he laments that pathology is usurping the place which, he thinks, should be occupied by practice and therapeutics. Though, he adds, one should avoid the therapeutic enthusiasm of the young dermatologist, who examined a recent patient as he lay on the autopsy table following a rigorous treatment which had cured a generalized skin condition, but killed the patient, with the remark, "Another day and there wouldn't have been a spot on him."

He also makes a point of the need for improved medical teaching, and urges that students be divided into small classes and that they be given much freedom in hospitals and dispensaries, under proper guidance.

He offers a good argument in favor of mid-wifery-- which, however, he would have in the hands of trained, licensed women,-- pointing out that the patients as a rule would prefer a female attendant, and that as the vast majority of cases are normal, it would be an enormous boon to the busy practitioner, especially in the country and in districts poorly provided with doctors. For, he adds, many more hours are spent in useless waiting, in running to alleviate false alarms, and so on, than can be computed. He firmly believed that such a measure would lengthen many a doctor's life. And at the end of the preface, he thoroughly and quickly muck-rakes quackery and "patent" medicines. His best known work, "Rab and his Friends" is a delicate sketch of a faithful dog, with the pathetic story of a case of advanced cancer of the breast operated by Syme, followed by infection, septicaemia and death of the dog's patient mistress, and later the death of her husband, heartbroken with grief. Rab's death closes the little tragedy, written in a simple and moving style. Another quaint study is Brown's collection of Majory Fleming's letters with a sketch of her life and a few other notes. This eight year old bundle of animated feminine precocity

was a daughter in a family with whom Sir Walter Scott was on most intimate terms; and she reckoned Scott as her most faithful lover, as he undoubtedly was. His grief at her untimely death, at a little over eight years of age, following measles, was proof of that. From her quaint letters, she must have been a remarkable little character; and it is due to Dr. Brown that these delightful bits of correspondence have been preserved. M. F. p. 93-94-96.

Sir Thomas Brown published his Religio Medici-- the religion, of faith, of a physician, under curious circumstances. He seems to have written out a set of pronouncements or dicta of religious and philosophical truths, for his own private interest and use; and these he showed to friends, and allowed them to be read and circulated among his acquaintances.

Through some one's meddling, an incorrect and imperfect copy, varying widely from the original, was published, and received wide circulation; and to off-set this, Brown brought out his work, that he might be placed in the proper light before the reading and thinking world of his day. The work is a heavy one, loaded with deep and original statements; it is well worth a slow and careful reading. R. M. Ch. ix; p. 117-118. xi; p. 120.